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A Monograph in

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AMERICAN LECTURES IN CHEST DISEASES

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Lung Cancer

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Dedicated to
LeRoy H Briggs

distinguished physician,
teacher, and friend

Introduction

By

J Arthur Myers

The recent phenomenal increase in knowledge of prevalence, diagnosis and treatment of cancer of the lungs has made imperative the preparation of a concise and practical volume containing all available facts concerning this disease His long, intensive study of pulmonary malignancy, his extensive clinical experience, his investigative spirit, and his vision of the solution of the problem have admirably qualified Seymour Farber for the preparation of such a volume

This monograph is the result of 10 years of constant study and observation in the field of bronchogenic carcinoma Such a period is almost nothing in the observation of persons with a lifetime disease like tuberculosis, but with cancer, which moves with such swiftness and usually kills with such promptness, a decade of observation is adequate to justify conclusions

The procedures here recommended and the conclusions drawn were based upon 1,070 autopsies which were carefully studied both clinically and pathologically These necropsies were performed in 19 California hospitals of all types, each employing a registered pathologist This insured broad and basic material In addition, 3,000 persons suspected of having lung cancer were admitted for cytological studies of sputum and bronchial secretions, along with other differential diagnostic procedures, in the laboratory of the University of California Hospital

One of the most important sources of material was the author's private practice, which provided an opportunity to study general practitioners' problems and viewpoints, as well as unique experiences in diagnosis and treatment of cancer. He first presents a broad pattern of etiology, histopathology, roentgenology, diagnostic aids and treatment for all cancer and then focuses on that of the lung.

This book is rightly directed to those in general practice, who compose the overwhelming majority of physicians throughout the world. It is they who most often have the opportunity to make the first examination of the individual who is developing cancer. Therefore, general practitioners are and must continue to be in the front line in the fight against this disease. In order to hold that line they must be adequately equipped with the latest techniques in diagnosis and treatment, as well as the best general information available. General practitioners, in turn, are the ideal group to transmit information concerning cancer to the public. This they do personally through the families of their clients, and through cancer control organizations. Without full cooperation of the public, further progress in the control of this condition will be slow.

With a relatively long silent period in its early evolution and with its host usually becoming aware of the presence of illness only after metastases have occurred, people everywhere should learn that cancer must be found before there are manifestations of illness if its victims are to be treated successfully.

The most serious handicap in the entire control movement is lack of a specific test to indicate the presence of the disease while the lesions are still microscopic, such as we now have in the tuberculin test for tuberculosis. Learning through such a test that cancer is present somewhere in a given individual's body, the physician

could make oft repeated examinations of those parts most frequented by this disease and locate the lesions as soon as they attain sufficient size to be detected Thus one might expect to locate and remove most cancers before they have metastasized While awaiting such a test for cancer, much can be done to improve the present situation

Although he recognizes that the only successful treatment of cancer today is surgical extirpation, the author, like many other workers in this field, has a deep conviction that the future treatment of pulmonary cancer will be with drugs Therefore he has outlined this complex field in such a way as to make all physicians more sensitive to developments in chemotherapy in the future

It is heartening to see emphasis placed upon the responsibility of physicians caring for persons who have inoperable or recurrent carcinomas At present, this constitutes at least 90 per cent of all who have cancer of the lungs It has been estimated that there are some 30,000 inoperable cases of bronchogenic carcinoma just in the United States The author says, "A real challenge to the physician's art is a patient who is inoperable at diagnosis or has post-operative recurrence" He then proceeds to present step by step the physician's armamentarium in coping with this situation

Dr Farber's extensive and long experience in the front line of the fight against cancer of the lungs, along with his constant teaching of formal medical school courses, lecturing before medical societies, presenting postgraduate courses for both specialists and physicians in general practice, and personal conversation with many practicing physicians have enabled him to grasp the needs of all physicians He has met these needs simply, concisely, and yet so completely that it is a privilege to speed this volume on its way to physicians everywhere

Acknowledgments

Because successful treatment of bronchogenic carcinoma is radical, and because of the complexity of the subject generally, it is sometimes assumed that the disease is a problem for specialists. It is, of course, a problem concerning many kinds of specialists, but it is also a clinical problem of great magnitude, the immediate concern of all engaging in the practice of medicine. The typical patient with lung cancer does not present himself at a cancer clinic, or a university hospital when symptoms first become apparent; he comes to medical attention routinely. This book has been written from the point of view, then, of the clinician, upon whose judgment other members of the medical profession must depend.

It is impossible to acknowledge all the obligations that are represented in a book of this kind. Every professional man with whom I have discussed the subject in the last 10 years has, in one way or another, contributed to this study. But there are special contributions which cannot be neglected. Drs. Mortimer A. Benioff, E. Fred Alston, Milton Rosenthal, James G. Tobias, Allen K. McGrath, Jr., Lloyd W. Espen, Walter H. Buel, Judith D. Smith, Jesselene H. Thomas, and Richard F. Barquist are, or have been, my colleagues in this study. They constitute the group without which this book could not have been written. Dr. Cameron Ward has generously given of his time in reading the manuscript. William Brandt, of the University of California English Department, has been assiduous in his numerous and valuable suggestions

for shaping the prose style toward maximum clarity and conciseness, and Miss Eleanor Little has checked the entire manuscript for conformity with established medical usage The aid of Dr Irving Reingold in securing photomicrographs is gratefully acknowledged Lastly, I should like to express my gratitude for the devotion displayed by my secretaries, Sadie Kaye and Jean Mulcahy Mistakes of one kind or another there must be in a book, but the co operation I have received has been of immense help in reducing such errors

S M F

Contents

Etiology | 1

THE MODERN physician is of necessity a practical man. If he has the inclination to master the complex theory characteristic of the advanced fields of medical research, he has not generally the time. His professional life is primarily concerned with people, not theory, and whatever view the scientist puts forward, the physician's interest in disease remains a therapeutic one, an interest in man's afflictions. His questions are always specific. With each patient his first question must be, What affliction? and his second, What can be done about it? The theory underlying a particular diagnosis and remedy is of secondary concern.

But all virtue to excess is vice, and the practicality of the physician can become impractical. A disease is not, after all, a collection of signs and symptoms responding uniformly to specific procedures. A disease is an abnormal process, a dynamic process brought about by exterior interference with normal function or by a specific physiologic disturbance. It has a cause, or coordinate causes. To approach disease from any less comprehensive point of view is to risk serious error. There are, of course, certain diseases, such as lobar pneumonia, in which a well marked "classic" appearance can be anticipated with some confidence. In such instances diagnosis can with some safety be a more or less routine evaluation of signs

and symptoms Few of the major diseases of the thoracic cage, however, are so regular in their progress that such a routine approach to diagnosis is possible Disease is conflict, and the symptoms and appearances that result are seldom specific enough to add up regularly and mechanically to the correct answer Consequently, the serious afflictions to which man is subject are very likely to be approached by a system of trial and error, a process of elimination which the patient does not always survive

The record of the medical profession in the diagnosis of bronchogenic carcinoma is regarded as unsatisfactory Our own findings are in conformity with published studies We have surveyed 1,070 cases of bronchogenic carcinoma, morphologically proven, collected from 19 hospitals in California * In 61 per cent of these cases, no positive diagnosis was made prior to autopsy Compared year by year, it apparently took as long to make a correct diagnosis of the disease in 1949 as it had in 1935 (Figure 7)

Most of this difficulty arises from the absence of any kind of "classic" case of bronchogenic carcinoma, its most common characteristic being its protean manifestations Thus, there is no available model form of the disease to serve as an accurate measure for diagnosis of the individual instance Surely in these 1,070 cases the possibility of bronchogenic carcinoma frequently occurred to the examining physician soon after the patient required medical attention, only to be rejected as unlikely on the basis

* The co operation and help of the pathologists and staff of the [illegible] acknowledged Birmingham V A Hos[illegible]nt Hospital French Hospital [illegible]ngeles County Hospital Let[illegible] Mt Zion Hospital Oakland V A Hospital Permanente Hospital San Francisco City and County Hospital San Joaquin County Hospital Santa Clara County Hospital Stanford University Hospital St Luke's Hospital University of California Hospital and Wadsworth V A Hospital

of inadequate signs and symptoms As a consequence diagnosis of the disease too often depended upon a protracted course of evaluation by elimination or other diagnostic possibilities

Barring an inovation in diagnostic technique any substantial improvement in the current diagnostic record requires a sounder approach to the disease Diagnosis requires an understanding of the disease process which underlies and gives rise to clinical appearances rather than a check list of signs and symptoms Such a basic approach can produce a much higher percentage of early diagnoses than are now obtained This approach requires some knowledge of and interest in the actual course of a disease beyond that which is visible to the eye and measurable by diagnostic techniques

The research workers interest is centered in etiology and pathology for improvement of techniques for controlling the disease the practicing physician must concern himself with the same subjects primarily for their service to diagnosis

The problem of bronchogenic carcinoma however cannot be isolated from the problems of malignancy in general and the whole subject is dependent upon our knowledge of normal physiologic behavior As has been pointed out many times the problem of cancer is ultimately a problem in tissue growth and the difficulties which arise when a coherent and comprehensive theory of cancer etiology is attempted reflect the complexity of normal cell development

Although there are still large gaps in our knowledge of the latter subject the general outlines of the process seem to be clear enough Most important to an understanding of malignancy is the well established fact that a normal fissionable cell (with which cancer research is especially concerned) does not have a single principle of

development and control Its course is governed by two distinct control mechanisms Basically, such a cell is limited in its potential development by its inherent structure which is determined ultimately by an enzyme or enzymes An undifferentiated cell may mature into one of several mature cell types, but the range is limited As an instance, the undifferentiated, basal cells of the bronchi may develop into ciliated epithelial cells, non ciliated epithelial cells or goblet cells In the presence of a mechanical or infectious irritation, such cells may approach squamous stratified epithelium But this completes the range of normal possibilities Every undifferentiated cell according to the "territory" in which it arises, has a similar selection of mature forms into which it may develop Such a development is irreversible, and a mature cell cannot itself divide

Upon these individual cells, already limited by their enzyme structure, the requirements of the whole organism are imposed *The operation of this secondary control* seems at times to be mechanical, but more important to such control is the complicated system of hormones and related substances which direct and integrate all bodily processes By this means the mature form that a particular cell will assume is determined Likewise, the needs of the organism as a whole determines the rate of production of undifferentiated cells, by fission, and the rate of maturation Both in clinical work and experiments with animals, it has proven virtually impossible to detect the precise nature of this hormonal activity It is an open *question whether an administered hormone* operates by direct operation in all instances or by the suppression of other and native substances However, there is reason to believe that the behavior of undifferentiated cells is generally determined by the total balance which is main

tained between several hormone type substances rather than by the operation of a single such substance

The development of malignancy requires that a cell or a group of cells escape to some extent the limits imposed by the needs of the organism and its normal environment Interest at the present time is chiefly centered upon the alteration of the cell itself This alteration is probably in the nature of a mutation The structure of a cell is composed of enzymes which convert body fluids to the needs of the particular cell and through which the cell performs its service to the organism as a whole For a cell to become malignant it is necessary that this basic enzyme pattern be altered without destruction of the cell In bronchogenic carcinoma as in cancer generally the malignant tissue often closely resembles normal tissue of the area in structure and in the microscopic appearance of the individual cells It is obvious that the alteration of the cell enzyme structure is a very limited one Something has been added or removed or altered so that the individual cell retains most of its properties perhaps even all of its properties except its self limiting one

Little is known about the details of the process by which the malignant transformation takes place Several investigators have confirmed the experimental supposition that the significant alteration takes place in the cytoplasm of the cell rather than in the nucleus Experimentally it has been found that a particular enzyme can be lost gradually in the course of several cell divisions However in most instances the transformation is presumably accomplished by the immediate effect of a substance exterior to the cell upon the particular enzymes responsible for cell growth The action of such a substance upon the enzyme is perhaps as specific as that of antibody upon microorganism Cancer producing substances are not only spe

cific for certain laboratory animals, and strains within the genus, but are very often active only in a particular organ of the affected animals Cancer arises as a result of an interaction between the specific tissue of the host and the carcinogenic agent

In human malignancy, cases are occasionally met in which one or the other of these two elements in cancer genesis clearly predominates Very often, however, it is difficult or impossible to make such a judgment So far as bronchogenic carcinoma is concerned, it is apparent that both elements share largely in the origins of the growth The pronounced age and sex predilections of bronchogenic carcinoma suggest just as clearly the importance of hormonal factors

Perhaps the relatively equal importance of these two elements is partly responsible for the fact that specific findings concerning the etiology of bronchogenic carcinoma are not always easy to relate to one another It must also be recognized that there is no reason to suppose that we will discover a *single* etiologic agent or etiological situation for the disease It must be anticipated that more and more etiologic agents for lung cancer will be demonstrated as time goes on, and it is possible that such agents will be found to operate toward the same end by radically different means

As a consequence, the etiology of bronchogenic carcinoma can best be organized by relating specific facts to the etiological theory to which they most clearly relate The first such theory is that bronchogenic carcinoma is in one way or another the result of an infection More widely held, at least in this country, is the theory that lung cancer arises as the result of chemical action upon cell structure These theories are not necessarily mutually exclusive, but each must be examined in its own right Quite distinct is the third problem of whether or not there

is such a chemical etiologic agent widespread in the environment, since this involves the question of rising incidence All of these theories and problems are related in some way to what must be the fourth consideration, the constitution of the individual upon which etiologic agents operate

INFECTION

A theory of infection for malignancy has always had the attraction of simplifying medical concepts, it brings cancer in line with other disease processes The theory had its secure beginning in the work of Rous, who isolated from chicken sarcoma a cell free filtrate with which he was able to transmit the disease It is generally assumed that the agent in the filtrate was a virus, although this has been disputed A similar filtrate has been demonstrated for a rabbit tumor by Shoup in 1931 The agent in this instance was almost certainly a virus, since the tumor was found to be epidemic among wild rabbits, it was obviously contagious Among wild rabbits, the resultant tumor was a benign papilloma, but when Shoup transmitted the virus by an acellular filtrate to laboratory animals, the tumor was malignant in a large percentage of instances This is the only instance so far uncovered of tumor contagion occurring in nature

Perhaps of more relevance to the concept of cancer genesis among human beings was the discovery of the milk factor" This agent was found accidentally during experiments which were primarily concerned with hereditary factors In experimenting with two strains of mice, one strain with a high incidence of mammary carcinoma among mature females, and another with a very low incidence, it was found by exchanging newborn females that the critical factor was not heredity but some filterable agent transmitted by the mother s milk The low incidence

female mice which had been nursed by females of the high incidence strain developed mammary cancer when mature, as did their descendants Again, this was presumed to be a virus

Further experimentation with "milk factor" carcinoma complicated the original findings by demonstrating that the hormone folliculin was also required for cancer genesis Female mice whose ovaries were removed before maturity did not develop mammary carcinoma even though they had been nursed by *females of the strains* carrying the milk factors On the other hand, male mice nursed by milk factor females developed mammary carcinoma if the hormone were administered It is assumed that the factor transmitting the disease passes into the bloodstream of the young animals and collects in the vicinity of the mammary glands, where it may remain in active indefinitely, unless folliculin in some way prepares the ground for the development of a malignancy This whole series of experiments provides an excellent illustration of the problems involved in the etiologic theory of cancer Does the virus require the hormone for activity? Or does the hormone act directly upon the potentially malignant cells and only indirectly upon the virus? We do not know

A great deal of experimentation has been directed toward the possibility of virus induced malignancies, but the three groups of experiments previously cited constitute the bulk of the evidence for the theory At the present time, most investigators seem inclined to regard the Rous chicken sarcoma, the rabbit papilloma, and the milk factor mammary carcinoma as exceptional situations having no parallel in human malignancy It is easier to assume that there exists in nature three exceptional viruses able to produce cell mutation in certain circumstances, than it is to adapt our experience with human malignancy to a theory of virus origin

There is, of course, no evidence that pulmonary carcinoma is of viral origin Where an etiologic agent has been indicated with reasonable certainty, it has been chemical If a viral agent were isolated in pulmonary carcinoma, it would probably be so ubiquitous as to lose much of its significance

Tuberculosis. All the evidence for a viral etiology for malignancy has been experimental, on the other hand, the possible importance of tuberculosis in the etiology of bronchogenic carcinoma depends entirely upon clinical observations The theory that there is a real connection between the two diseases is an old one, and it has suffered many vicissitudes Ewing at one time believed that tuberculosis would eventually prove to be the most important single etiologic agent in bronchogenic carcinoma When large scale autopsy studies made it apparent that tuberculosis could not possibly fill this role, it was often somewhat hastily assumed that it had no significance to malignancy studies at all An opposing theory was even advanced which suggested that there was some kind of antagonism between the two diseases, so that the tuberculous patient could at least be given the doubtful assurance that he had acquired some kind of immunity against lung cancer

Statistical studies are inconclusive De la Fuente found only 34 cases of coexistent tuberculosis and carcinoma in 2,500 autopsies at Sea View Hospital On the other hand, some investigators have found impressive percentages of coexistence Fried found 34 cases of coexistent tuberculosis in 319 autopsies where the primary diagnosis was lung cancer It is very difficult to determine the relationship between two such processes in individual instances, and it may be that the high percentage of coexistence that Fried found is to be accounted for by reactivation of old tuberculous lesions So long as malignancy was regarded as a kind of catastrophic destruction or alteration of a cellular enzyme pattern, the effect of a chronic condi-

tion such as tuberculosis was of dubious importance Recent studies in cell physiology suggest however that permanent alteration can be achieved gradually that an enzyme may be eliminated through a series of cell divisions perhaps when such division is excessive If this is the case the local imbalance resulting from pulmonary tuberculosis may occasionally result in malignancy We do not have sufficient evidence for accepting or rejecting the possibility

In any case coexistence of tuberculosis and cancer is a diagnostic problem of importance There has been a sharp increase in the proportion of the tuberculous population who are over 40 years of age as this trend develops the problem of coexistence will become increasingly serious So long as we routinely check for tuberculosis and not for carcinoma there will remain the tendency to treat a patient for the former while he is dying of cancer

Chronic infections The rationale for proposing any chronic lung infection as an etiologic agent in bronchogenic carcinoma is much the same as the rationale for proposing tuberculosis although each infection must be established or disproved in its own right There is of course almost invariably some kind of infection secondary to a lung tumor Where carcinoma is discovered during the treatment of infection the malignancy can be generally demonstrated to be antecedent Nevertheless it is not safe to assume that the situation cannot in certain instances be reversed we are not justified in positively rejecting chronic infection as a possible factor in the etiology of bronchogenic carcinoma

CHEMICAL IRRITANTS

This class of possible etiologic agents is large and it has attracted much attention both in the clinic and in the laboratory Again the underlying supposition for a long

time, was that a chronic metaplasia, induced by what was essentially an irritant, could, in a certain number of instances, progress to a frank malignancy The earlier work on cell physiology tended to discredit this view, at the present time it is again of interest because it has been found experimentally that excessive cell division can occasionally alter the enzyme pattern of a cell permanently

However, most chemical agents which have been proven to be of etiological significance to malignancy are thought to operate in a different manner They would seem to modify cell structure directly Although they can be accompanied by an irritative effect, this is not a necessary part of their action, and certain of them have no detectable irritant action at all They are carcinogens

The idea was developed out of the finding of Yamagiwa and Ichikawa that repeated applications of coal tar to the ears of rabbits led to the development of malignancy at the site of application This was confirmed in numerous experiments with mice, and in 1930 a London group directed by Kennaway first isolated a purified product from tar (benzpyrene) which was very active in inducing carcinoma In the next few years, several hundred such hydrocarbons of varying degrees of effectiveness in inducing malignancy were discovered It was during these subsequent experiments that it was found that inflammation was a side effect to the carcinogenic action The ability of a compound to induce cancer did not correlate with its inflammatory properties

It was also apparent that the effect of the carcinogen was sometimes quite specific While some compounds induced malignancy at the site of application, others showed a consistent predilection for a particular organ of the body, regardless of the route or site of administration As early as 1925, Murphy and Sturm had come to the conclusion that the high percentage of bronchogenic carcinoma

which they had observed in mice painted cutaneously with coal tar was not the result of inhalation of fumes as had been supposed It was, they concluded, the reaction of bronchial tissue to the systemic effects of the tar Then, methylcholanthrene was developed With this substance it proved possible to elicit bronchogenic carcinoma in mice by any method of administration subcutaneously, intravenously, intraperitoneally, orally, or by local application

These discoveries have unfortunately become more complicated rather than simplified with time The carcinogens in the earlier experiments were a group of hydrocarbons with closely related molecular structures, and it seemed for a time that the carcinogenic action was to be accounted for simply in terms of such structures Thereafter, however, totally unrelated substances were found to be likewise carcinogenic

It is, nevertheless, tentatively assumed that the carcinogenic properties of such substances arise from a similar effect upon cells The studies of Miller and Miller have been particularly relevant to the question of how such substances operate These workers found that p dimethyl aminoazobenzene when administered to rats bound itself tightly to certain proteins of the liver cells, but did not affect the cells of other organs This susbtance almost invariably produces carcinoma of the liver Subsequent experiments have tended to confirm the supposition that carcinogens which have a predilection for a particular organ are in some way collected and bound by the cells of that organ Such substances apparently unite with the enzyme or enzymes effecting cell growth without destroying the cell itself

The transformation from normal growth to malignant growth is in the nature of a mutation Not only does the

transformation parallel gene mutation in many ways, it seems at times to be virtually an identical process That x ray radiation can be used to induce genetic mutation, and that it may, in certain circumstances, lead to the development of malignancy, is well known It has further been demonstrated that several of the highly carcinogenic hydrocarbons are likewise potent agents in producing genetic mutation Mustard gas has carcinogenic properties in addition to its well-known action in inducing mutations Between two such specific processes there is not, of course, a one-to one relationship However, there is a substantial degree of correlation, and it is reasonable to assume the processes are not dissimilar

Another experimental observation should perhaps be mentioned although its significance to cancer theory is by no means clear Several of the substances which are known to be carcinogenic under certain circumstances may, under other conditions be useful as agents in the treatment of malignancy Again, x ray radiation is the best illustration of this dual function, but mustard gas shows the same range of effects Urethane, which is used in the treatment of chronic leukemia, has also been demonstrated to be a carcinogen, leading to pulmonary malignancy in mice

Our knowledge of carcinogens and the way in which they operate is derived largely from work in the laboratory, and the extension of theory from experiment to nature must be made cautiously However, there seems no good reason to doubt that the pulmonary malignancies found in chromate industry workers and pitchblende miners as described later, are the result of a carcinogen in an industrial environment Other situations are more doubtful We are probably justified in assuming a carcinogenic effect when in nature a substance is found to give

rise to carcinoma, on the other hand, it is possible that such agents may eventually be shown to have a different mode of operation at different times

Schneeberg-Jachymov radiation. One of the earliest instances in which cancer was found to be an industrial hazard was the discovery of an inordinate amount of lung cancer among the miners of Schneeberg Although the ore from this mine contained silica, bismuth, nickel and arsenic, it is generally agreed that the agent responsible for the high incidence of malignancies is pitchblende The disease is thus the result of prolonged, although moderate exposure to radiation, and the mode of operation is compatible with the theory of carcinogen

The percentage of miners succumbing to lung cancer is quite high In 1935 Lange found that between 60 and 70 per cent of all miners at Schneeberg died of bronchogenic carcinoma, this rate has apparently existed for several hundred years At Jachymov, where the diagnosis was made much later, 18 of 25 autopsies between 1929 and 1931 revealed the same condition It is to be noted that although the whole body, and particularly the skin, is exposed to radiation the high rate of malignancy is exclusively pulmonary

Chromium Pfeil added this mineral to the list of industrial carcinogens as recently as 1935 Although the total number of cases so far reported has been small, in the situations investigated, the carcinogenic action of chromium would seem to be a powerful one Machle and Gregorious surveyed 193 deaths among chromate workers 66 of these men died of cancer It did not appear to be as specific for the lungs as pitchblende, but the lungs were affected far more frequently than any other organ

The studies thus far reported are sufficient to indict some element in the environment of chromate workers as definitely carcinogenic The history of such employment

hence becomes a significant fact in diagnosing chest disease Thus far however, neither chromium nor its compounds has been proven in the laboratory to be carcinogenic This might mean that something else in the environment of these workers is the specific carcinogen On the other hand species is so important to carcinogenic action that chromates may be carcinogenic for human beings even though they are inert for laboratory animals

Silicosis When free silica penetrates the alveoli and smaller bronchioles of the lung it stimulates connective tissue cells When the silica is present in sufficient quantity over a considerable period of time silicosis results However silica is chemically one of the most inert compounds in nature and it is not believed to have any effect upon the epithelial elements in which bronchogenic carcinoma arises Nevertheless it has been suggested that a history of silicosis is of some significance in malignancy In 1932 Fried reported finding at autopsy a very small bronchogenic carcinoma associated with pneumoconiosis and extensive metaplasia Charr found bronchogenic carcinoma in the autopsy studies of 36 cases of silicosis Klotz found four tumors in autopsying 50 cases Such findings are not conclusive of a relationship but they are suggestive Perhaps some substance commonly associated with silica in small amounts will on future study prove to be carcinogenic it seems doubtful that silica itself will ever be found to have such an effect

Other industrial hazards There have been numerous other industrial products suggested as possible agents in the genesis of bronchogenic carcinoma but studies to date have been inconclusive Homburger at Yale Medical

of nickel copper refineries are somewhat more predisposed

to bronchial malignancy than the population at large Arsenic is known to be carcinogenic when it is in prolonged contact with the superficial epithelium perhaps it predilects to bronchogenic carcinoma when it is inhaled as dust *It is not unlikely that other substances* found in certain industrial situations will be proven to be of significance in the etiology of bronchogenic carcinoma

NON-OCCUPATIONAL CARCINOGENS AND THE QUESTION OF INCIDENCE

It has been possible to show a convincing etiological relationship between certain specific exposures and bronchogenic carcinoma, because something approximating a controlled situation exists in the investigated industrial situation Where the hazard is not occupational, statistical evidence is more difficult to evaluate Nevertheless many investigators have for a long time believed that there are one or more agents in our general environment *which* predicate to bronchogenic carcinoma This conclusion is based in large part upon the conviction that there has been in recent years a real rise in incidence of the disease, and it is reasonable only if such an increased incidence *is believed to exist*

This question of rising incidence is perhaps the most debated in contemporary medicine The basic fact is that every large collection of cancer statistics in the last twenty-five years has shown a steady increase in the number of cases of bronchogenic carcinoma which are found yearly In the Trioph and Holland study at New Orleans, nine bronchogenic carcinomas were found at autopsy between January, 1918 and January, 1928, between the latter date and July, 1938, 186 such cancers were reported in the same institution Similarly, in the tabulation of 10 000 autopsies at Johns Hopkins Hospital from 1896 to 1930, MacCallum found about a five-fold increase be

tween the first and last decades of the study All studies over a comparable period of time show about the same rate of increase

The question at the present time is whether or not this increase is a real and not a statistical one So astute a student of the subject as Fried for instance as recently as 1948 concluded that this apparent increase was an illusion There are four major factors which must be taken into account in evaluating such studies We cannot estimate the effect of any one of them with any precision

(1) The first is simply the increased interest in the condition We tend to find a disease such as bronchogenic carcinoma in proportion to our willingness to look for it The publicity that the disease has received in the last 20 years is in itself sufficient to effect the reported incidence

(2) Incidence is certain to rise as diagnostic methods are improved Some of this apparent increase is to be accounted for by the increased use of x ray bronchoscope and microscope

(3) Chemotherapy has undoubtedly played some part in the apparent increase of malignancy In many instances today we are able to diagnose bronchogenic carcinoma because confusing secondary infections are at least temporarily cleared by the new drugs exposing the tumor body to roentgenologic view There can be no question that many of the patients of 20 years ago who were thought to suffer from some chronic lung infection actually expired as a result of an undiagnosed bronchogenic carcinoma

(4) The last major factor to be considered is the steady increase in longevity Cancer of the lung being primarily a disease of middle age it follows that as a greater percentage of the population reaches this cancer age the number of cases of cancer will increase The in

creased incidence to be anticipated each year from this aging of the population is small, but none the less real

These four elements are of importance in estimating the current status of cancer of the lung and they have undoubtedly accounted for some of this apparent increase It does not follow, however, that after these have been allowed for, there may not be a sizeable residue of increase which represents a genuine rise in incidence It is easy to see an increased medical efficiency and an aging population as responsible for the steady increase in incidence from 1900 to 1940 These two factors are not clearly adequate for the persistence of this increase over shorter periods in the last few years The report of the Public Health Service, from death certificates, shows a radical and constant increase in the number of bronchogenic carcinomas from 1930 to 1940 Perhaps this may be adequately accounted for by better diagnostic facilities and an aging population But it is very doubtful that these reasons can account for all of the surprisingly consistent increase for each year from 1940 to 1945 Steiner, on the basis of an examination of 36,864 autopsies made at Los Angeles County Hospital between 1918 and 1946 concluded that there had been a real and absolute increase in incidence during this period From 1923 to 1927, carcinoma of the lung was found in 0 6 per cent of all autopsies and constituted 4 3 per cent of all malignancies Between 1943 and 1946 this disease was found in 2 3 per cent of all autopsies and accounted for 11 3 per cent of all malignancies This increase was not accounted for by a changing sex ratio nor was there an increase in cancer of the large intestine or pancreas None of the factors to which rising incidence has been attributed seem significant upon close inspection

Most recent studies with smaller groups point in the same direction In a comparison of bronchogenic carci

noma with carcinoma of the stomach, larynx and bladder, Ariel, *et al*, found the former increasing relative to the other types In 1931 bronchogenic carcinoma comprised 2 1 per cent of all cancers diagnosed, in 1946 it was 11 7 per cent Gastric cancer, which shows about the same age incidence, showed no significant increase, thus minimizing the possibility that a change in the character of the hospital population was of much importance Fulton found a regular increase in Liverpool from 1944 to 1948, from 145 per million population to 207 per million

Perhaps it is safe to say that 95 per cent of recent statistics bearing on this question suggest that there has been a real increase in lung cancer Of the studies which point in the other direction, that of Clemmenson and Busk in 1947 (*Brit J Cancer*), would seem to carry a good deal of weight They compared the figures for Denmark at large with the findings of the Central Tuberculosis Station of Copenhagen where superior diagnostic methods had been in use They found that in the latter situation there had been only a very slight increase in bronchogenic carcinoma between 1936 and 1945, while in the country at large they found a rise comparable to that reported elsewhere Further they found in the population at large that the ratio of men to women with the disease increased in this period from 5 4 to 3 1 During the same period the sex ratio in the Central Tuberculosis Station remained virtually constant at about 8 1 They concluded that the apparent increase in lung mortality is, to a very large extent conditioned by improvements in diagnostic means, and it can be expected to continue until the sex ratio amounts to about eight males to one female

Incidence is not a subject upon which one can dogmatize safely but it is obvious that the weight of evidence favors the presumption of a real increase The Copenhagen study is impressive, but not conclusive It runs

counter to the general observation that the greatest increase to this time has been reported in urban areas, and it is by no means clear why diagnostic facilities should affect the sex ratio This altering ratio would seem, in fact, to mitigate against the conclusion expressed

It is the author's opinion at the present time that there has been a real increase in the incidence of lung cancer, and further, that we must expect the present rate of increase to be continued If bronchogenic carcinoma is not already the most common form of malignancy in males, it can be expected to assume this position within the few years We also anticipate a sizeable increase in incidence among females

Smoking If there has been a genuine increase in bronchogenic carcinoma beyond that accounted for in terms of an aging population, it would seem that it should be attributed to some changing element, or elements, in the environment of modern man It is doubtful that the whole range of industrial hazards is sufficient to account for 1 per cent of the carcinomas reported yearly, these industrial hazards are not likely to have any marked influence upon national statistics If there is a real increase in the incidence of cancer, it implies some very wide spread carcinogen, transcending occupational hazards Of such potential agents, tobacco smoke is the nearest to common acceptance

Adler was the first to suggest that tobacco might be etiologically significant, there has been since that time a steady series of reports on the question Most recently Schrek, *et al*, found evidence of a real relationship, and Wynder and Graham published a study of 684 cases of proved bronchogenic carcinoma with a major effort to provide proper controls Their conclusion was that 'excessive and prolonged use of tobacco, especially cigarettes, seems to be an important factor in the induction of bron

chogenic carcinoma " They found that 96 5 per cent of 605 men with bronchogenic carcinoma had smoked more than 10 cigarettes a day for 20 years or more as compared with only 73 7 per cent smoking this quantity among the cancer free controls About 85 per cent of the patients with cancer in this series had been smoking for 30 years or more Over half the patients with the disease were chain smokers consuming 35 or more cigarettes daily as compared with only 19 per cent chain smokers among the controls Breslow of the California Public Health Service carefully correlated smokers and non smokers in a very thorough study in which histories were taken by specially trained investigators His conclusion was similar to that of Graham and Wynder he found a consistent correlation between lung cancer and cigarette smoking Lung cancer can and does occur in non smokers but it is about two and a half times as frequent among those who smoke cigarettes in significant amounts

Opposition to the theory of the carcinogenic action of cigarettes depends to a great extent upon experimental work No carcinogen has been demonstrated in work with tobacco products Tobacco tar applied to the skin of mice has been of no effect Flory has produced papillomas with distillations of tobacco tar but they did not become carcinomatous This negative evidence admittedly is not conclusive a substance which is carcinogenic for one species is frequently harmless for another Also inconclusive though interesting is the finding of Fried that studies of lungs of heavy smokers failed to reveal changes in bronchi or pulmonary parenchyma that could be attributed to heavy smoking

Most investigators particularly since the work of Wynder and Graham seem inclined to accept cigarette smoking as predilecting to bronchogenic carcinoma Whether the carcinogen is one of the tars in such smoke

or arises from the burning paper, is not known It is also not certain that the agent, if any, is a true carcinogen It is possible that bronchogenic carcinoma arises as the result of an atypical and protracted reaction of the host to some normally harmless constitutent of the smoke Every doctor is familiar with the problem of the relation of smoking to chronic and non-specific ill health A certain percentage of such patients can be "cured" by withdrawing their cigarettes, others presenting themselves with very similar symptoms are not helped by such a withdrawal It is tempting to see in the responses of the first group of patients something very like an allergy It is further tempting to see in them potential victims of bronchogenic carcinoma As numerous writers have pointed out, the diagnosis of this carcinoma is frequently complicated by a long history of chronic and usually atypical lung disturbances In our own experience, patients with bronchogenic carcinoma very frequently present a history compatible with a chronic and comparatively mild bronchial allergy, which in many instances seems to be due to the habitual use of tobacco

Petroleum products. It may be that the lavish use of tar and petroleum oils, so characteristic of modern culture, will finally prove to be more important in the genesis of bronchogenic carcinoma than smoking The agents most commonly suspected in this general indictment so far have been road dust containing tar, gasoline fumes and exhaust fumes from automobiles, and industrial fumes If they are proven to have carcinogenic properties, their increasing prevalence in the modern landscape would be sufficient without anything else, to account for the rapidly increasing incidence of pulmonary malignancy

The basic experimental work with regard to these agents was that of Campbell, who elicited pulmonary tumors in 74 per cent of a group of mice exposed to road

dust containing two to three per cent tar only 14 per cent of his controls developed the disease There is further some clinical support for the theory Mountin and Dorn in a public health survey in 1939 found a higher proportion of bronchogenic carcinoma in urban dwellers than in a similar age group of the rural population Public Health surveys consistently report substantial differences in incidence between industrial and rural areas

Similar studies in England come to the same conclusion with perhaps more authority since in these studies the influence of varying climatic conditions shifting population and differences in diagnostic facilities is apparently at a minimum In the most recent of these studies that of J S Fulton covering the years 1944 to 1948 found a pronounced difference between urban incidence in Liverpool and the rural incidence within a comparatively surrounding small area In the heavily industrial areas incidence was about 27 cases per 100 000 population In three rural areas the figure was three eight and 10 cases per 100 000 Fulton believed that these figures reflected a real and substantial difference in incidence between the two groups This difference in incidence very possibly results from varying degrees of exposure to air containing petroleum products

METABOLISM AND HEREDITY

Although the relationship between exogenous agents and the native constitution of the individual to date has proven to be almost impenetrable it is obvious that constitutional factors are important Many men have spent long lives in the most carcinogenic of environments—in the Schneeberg mines for instance and died full of years and absolutely free of any evidence of bronchogenic malignancy

At one time interest in the relationship of malignancy

to the native constitution of the individual centered on the theory of microscopic "cell rests" of embryonic tissue which remained quiescent into adult life, but which could become suddenly active and malignant This theory has been generally abandoned as a comprehensive account of malignancy, but some clinicians would still see undifferentiated and/or adenocarcinoma as the product of such rests The difficulty is that such cell rests have never been demonstrated Further, most pathologists are doubtful of an etiologic theory which proposes a separate origin for the different lung cancer cell types, since most lung tumors show a mixture of such cell types, and frequently all possible variations will be found in different parts of the same tumor

The present tendency is to see the important factor of "native constitution" as reflecting the complicated system of hormones and related substances which govern physiology The importance of such compounds in the genesis of carcinoma of certain tissues is well established To instance one example out of many, it is well known that men who receive diethylstilbestrol over a long period of time are subject to a higher incidence of mammary carcinoma

Although laboratory findings are not entirely consistent, in general it has been found that the administration of sex hormones are apt to induce malignant growths only in sex-hormone conditioned areas It is possible that such tumors are somewhat exceptional in their genesis Tumors can sometimes be induced in other organs or areas of the body by the administration of hormones, but such growths are commonly benign Lipschutz, in his work with guinea pigs, found that peritoneal growths never progressed to malignancy In human beings, benign growths seem generally to be more susceptible to malignant degeneration than normal tissue

Again, then, there seems to be a situation which can only be explained in terms of two factors cooperating to produce malignancy The hormonal factor would seem to be overwhelmingly important in the genesis of tumors of the sex-conditioned areas—mammary, testicular, prostate tumors, and so forth But such a factor is also very clearly indicated in tumors of other parts of the body, although the effect of this hormonal factor seems to be secondary to that of the exogenous carcinogen Age and sex predilections are convincing evidence of the influence of hormones upon the genesis of bronchogenic carcinoma (Figure 1)

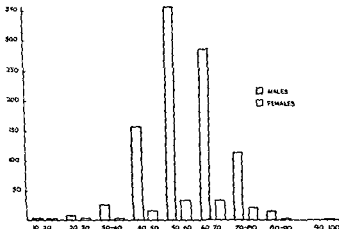


Figure 1 Age and sex distribution of 1 070 patients with bronchogenic Ca

This predilection for age groups above 40 would seem almost certainly to indicate a general physiological condition as a prerequisite for the disease The overwhelming proportion of men among the patients with bronchogenic carcinoma points the same direction It seems most unlikely that cigarettes or other specialized environmental

influences can account for a 9:1 sex ratio, although they may influence it.

At least as important as this statistical evidence is the long interval that is frequently encountered between exposure to a known carcinogen and the development of the pulmonary malignancy. In many of the cases found among the Schneeberg-Jachymov miners, the disease developed from six to nine years after retirement. A similar situation exists among cigarette smokers, malignancy not infrequently appears some years after smoking has been discontinued. It is possible that this interval represents a delayed reaction to the carcinogen, it may be that the appearance of the malignancy can be delayed for years after the process is initiated. This explanation is, however, the least likely one, it is far more reasonable to assume that the process initiated by the carcinogen requires a particular hormonal substrata for the development of malignancy. Although no specific bodily substance has even been suggested as critical to the genesis of bronchogenic carcinoma, clinical evidence, supported by experimental and statistical findings, makes it probable that some such substance exists.

Heredity. Whether or not heredity is an important factor in the genesis of bronchogenic carcinoma would seem to be at this time a secondary problem. Unless the embryonic cell rest thesis is established, which seems improbable, heredity is not apt to become the critical problem to lung cancer etiology. Although laboratory work on this subject is of interest, it is not conclusive. It is well known that strains of mice have been bred which will predictably develop bronchogenic carcinoma almost 100 per cent of the time. This does not prove that bronchial malignancy is a hereditary disease, as the latter term is usually defined. If the etiology of lung cancer involves a dynamic relationship between host and carcinogenic

agent as much clinical and experimental work suggests it need not occasion surprise that hosts can be developed which virtually eliminate the necessity for an exogenous agent The general view is not contradicted by such a finding

Experimental work on this subject is dependent then upon an understanding of the relationship of the host to the tumor—a subject which as has been said is admittedly not understood Further the clinical approach that seems open at the present time has been largely unexplored The few studies that have been attempted so far on possible differences in racial susceptibility have been insufficiently controlled The earlier impression that bronchogenic cancer was a characteristic of civilized races has been denied by French workers in North Africa There have been to our knowledge no statistics from Asiatic nations which might be compared to European or American statistics with any confidence

There is some important but inconclusive evidence that in the United States the Negro is perhaps somewhat less susceptible to bronchogenic carcinoma than the Caucasian Ochsner found the ratio of white to Negro patients admitted to New Orleans Charity Hospital for cancer of the stomach to be about 2 3 similar to the all admission ratio But the ratio was about 2 1 for bronchogenic carcinoma Arkin and Wagner found a similar picture at Cook County Hospital with Negroes accounting for 30 per cent of all admissions and only 9 per cent of all cases of bronchogenic carcinoma The difficulty with such studies is that they are not able to take into account the diagnosis environmental and longevity differences that perhaps exist between the two races It seems possible that there is a substantial difference between the races in susceptibility to bronchogenic carcinoma but very carefully controlled and evaluated studies are necessary to

prove these differences The same conclusion must apply to our own finding, following Steiner, of a pronouncedly different sex-ratio between white and Mexican patients, the latter showing about three males to two females with this disease as compared to the 8 1 sex ratio for the whole series

It must be emphasized that these findings are really inconclusive, the suggestion that heredity is an important factor in the disease cannot be discarded on the basis of our present evidence Strong hereditary factors are thought to be operative in other forms of neoplasms, particularly xeroderma pigmentosum, neuroblastoma of the retina and multiple polyposis of the colon, and hereditary factors may well be operative in bronchogenic carcinoma It may further be pointed out that if heredity is established so firmly as to be significant to such diagnosis, the hereditary factor can be expected to be quite specific It is unlikely that a familial history of other forms of malignancy will ever be of especial significance in the diagnosis of lung cancer

No review of the etiology of bronchogenic carcinoma can be definitive Our information simply does not add up to a coherent system that can be neatly summarized Almost every major finding can be confronted with an other experiment, or another clinical observation, which seems to suggest a contradictory conclusion Most markedly, in bronchogenic carcinoma there is considerable difficulty in adjusting clinical to experimental evidence, and either kind of information, when unsupported by the other, lacks authority

It seems most likely that bronchogenic carcinoma is the product of two more or less independent series of events The process appears to begin with an irreversible alteration of structure in a cell or a group of cells The possibility that chronic irritation can, by itself, lead to

such an alteration must be kept in mind but this has not been established clinically It is certain that particular agents can and do accomplish this transformation by direct action upon cell structure these agents are carcinogens whatever their specific nature It has been proven that there are many such carcinogens in nature investigators generally assume that they operate in essentially the same manner

The second condition required for the development of bronchogenic carcinoma seems to be the weakening or elimination of the intracellular mechanisms of the area or of the whole organism which limit growth of units of cells to a functioning relationship with the rest of the organism The long interval that is frequently noted between exposure to a known carcinogen and the development of a tumor is to our mind overwhelming evidence that the human organism is usually able to inhibit the growth of abnormal cells

It is conceivable of course that the cell mutation depends upon the altered hormonal substrata for its accomplishment but it is difficult to see how a carcinogenic action could remain potential for long years except by an already altered cell This is an area where there is little direct evidence to support any theory but it seems most reasonable to assume that the carcinogen accomplishes the cell alteration shortly after exposure the development of the frank malignancy then must await the development of a suitable environment It is known that microscopic cervical malignancies can be quiescent for years and prostatic cancers apparently have the same property These clinical findings may justify the assumption that a similar situation exists in the case of bronchogenic carcinoma

It is necessary to modify even so general a description by recognizing again that these transformations are not absolute but relative Even within such an apparently

distinct and comparatively homogeneous form of malignancy as bronchogenic carcinoma, it is obvious that these two processes do not bear a consistent relationship to each other or the malignant growth *Where the disease occurs in children, it seems that the dominant consideration is the hormonal one* In other individual instances the clinician frequently gets the impression that there is no *native resistance to the growth In radiation exposure,* on the other hand, the exogenous, carcinogenic factor is obviously dominant Perhaps in all cases, both factors are in play, but they do not have a consistent relationship to one another

This is hardly an exact etiological description of bronchogenic carcinoma, since even so much leaves evidence out of account Nevertheless, we are accumulating facts, and from these facts we are able to build hypotheses in the way that has been so fruitful for the sciences generally Much remains to be learned, but moderate optimism *is not out of place We are making progress toward* an understanding of the disease

Histopathology | 2

At least some of the obscurity in which the etiology of bronchogenic carcinoma is currently hidden results from our imperfect understanding of the histopathology of the disease Few tumors are so markedly pleomorphic as those found in the lung Not only does microscopic appearance vary widely from one tumor of the lung to another but also equally wide variation is very often observed within a single tumor In spite of this inconsistency however morphologic studies would seem to be of real importance Even though the morphologic distinction between lung tumors is imprecise it is usually possible to describe the individual tumor in terms of a predominant cell type In statistical studies of case histories in which such morphologic distinctions have been attempted the findings suggest that the predominant cell type possibly reflects an etiologic situation distinct from that of other cell types There are sex and perhaps age predilection differences between one cell type and another Such cell types seem also to affect tumor location tumor behaviour and prognosis

At the present time we do not have sufficient information available to evaluate these differences authoritatively The conclusions derived from collections of case histories are tentative because the individual case histories are so often inadequate in regard to histologic structure Death

certificates should include more exact information, includ ing predominant cell type and primary location whenever these facts are available Every tumor case coming to autopsy should be carefully analyzed in terms of its mor phology, with particular attention to the cell type at the point of origin This is a responsibility of the entire pro fession

A prior necessity to improved reporting of lung cancer cases is a morphologic classification for these lung tumors which will be etiologically and clinically significant and *easily determinable histologically Such a classification* seems to be at hand Most students are now willing to accept a three fold division of the bronchial tree malig nancies into squamous carcinoma, adenocarcinoma and undifferentiated carcinoma The distinction of squamous cell carcinoma from the other two types seems to be ac cepted generally, but it has been denied that there is a significant distinction between adenocarcinoma and un differentiated carcinoma Womack and Graham have for a long time denied the significance of such a division, and most recently, Reinhoff did not attempt to separate the two cell types On the other hand, most workers feel that there *is* a striking difference in the microscopic appear-ance between the two classifications Adenocarcinoma and mixed cell types are perhaps found in conjunction more often than either is found with squamous carcinoma, but this is not a marked tendency Further, there seems to be a significant statistical distinction between the two cell *forms in most studies*

The opposition to their separation seems to arise, to some extent at least, from etiologic theory Womack and Graham believe that squamous cell carcinoma is pro duced by exposure to carcinogens, and that other com mon lung tumors arise from fetal buds in the bronchi (Chapter I) The distinction between adenocarcinoma

and undifferentiated carcinoma may prove in time to be an artificial one but clinical evidence cannot be organized to suit etiologic theory In our judgment there is sufficient evidence to justify the distinction between adenocarcinoma and undifferentiated carcinoma

Other classifications have been suggested from time to time At the beginning of the century most lung cancers were reported as sarcomas Although these tumors were actually carcinomas a bronchogenic sarcoma is not an impossibility Black in a survey of literature on the subject found six substantiated instances of sarcoma already reported and added one more The malignancy is characterized by exceptionally slow growth usually in and around the bronchi by late and limited metastasis and by marked sensitivity to roentgen ray therapy

There is also possibly a distinct alveolar cancer Smith Knutson and Watson have recently reported 20 cases which they described as Terminal Bronchiolar or Alveolar Cell Cancer of the Lung They found the tumor distinguished by a malignant epithelial lining of the alveoli without pronounced bronchial involvement The difficulty is in establishing an origin for such a growth Miller did not find an epithelial lining in normal bronchi Fried believed there was such a lining Even if Fried is right however one cannot assume that these presumably fully developed cells have the possibility of a malignant transformation Many students believe that the alveolar cell carcinoma is actually an atypical development of the squamous cell

PATHOLOGIC CLASSIFICATION

Lung cancers cannot ordinarily be distinguished one from another on the basis of their gross appearance These tumors tend to be hard and granular and white gray or pink in cross section Squamous cell carcinoma is more

EARLY ASPECTS OF MALIGNANCY

Each of the common forms of bronchogenic carcinoma has a readily apparent relationship to normal tissue of the trachea and the bronchi. According to Miller, there are four distinct cell groups to be considered in the tracheobronchial tree. These are the basal cells, situated just

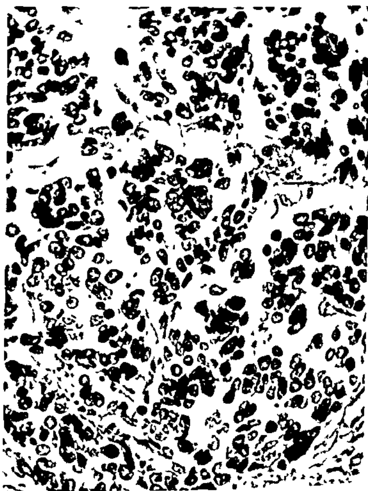


Figure 5

above the basement membrane the intermediate cells lying on top of the basal cells ciliated epithelial cells which constitute the lining of the structure and mucous producing goblet cells which are found interspersed among the ciliated cells As the bronchi approach the terminal alveoli the goblet cells gradually disappear and the ciliated cells lose their cilia without any other major modification of cell structure These four normal cell types are in microscopic appearance obviously related to the malignant transformation of the normal cells which they resembled It is most unlikely however that the fully developed goblet or the ciliated epithelial cells have the potentiality of further development which would make them capable of division Instead pathologists generally regard the multi potential basal cell as the origin of all new growth in the bronchi normal or malignant Thus these common forms of lung malignancy would be the result of an abberation basically the same in all instances but involving minor differences affecting the rate of cell division and so forth There could readily be in such a situation different forms of malignancy with different clinical and morphological characteristics but these distinctions would not of necessity be sharp ones There remains the possibility of course that one form of cancer or another arises from embryonic rests as mentioned in Chapter I

Evidence concerning the beginning of malignancy in the human lung is naturally scant In a series of routine lung sections Petersen Hunter and Sneeden found five minute growths which they regarded as definitely carcinomatous Further studies were inconclusive with regard to such major questions as the origin of malignancy Perhaps the most significant observation of these workers was that four of these five growths were found in conjunction with bronchiectasis and fibrosis Autopsy reports

on small tumors have been made in sufficient numbers to suggest that, if pulmonary malignancy does not originate in areas of metaplasia, it begins with an aberrant metaplastic piling up of the epithelium Experiments with laboratory animals have been inconclusive with regard to the beginnings of a tumor

The complexity of the modern view of cancer growth has been discussed in the first chapter, practically all of the original theories have had to be abandoned for highly qualified concepts There has likewise been some modification of our basic definition of malignancy as autonomous and irreversible growth Because clinically-observed cancers were characterized by steady enlargement, it was assumed that malignancy was a process which, once initiated, proceeded without delay and irreversibly to the destruction of the host However, it has been discovered that even large tumors are sometimes dependent upon the maintenance of a certain hormonal substrata for continued development, prostate tumors can be arrested for long periods of time, although not permanently, by the administration of female sex hormones More spectacular is the recent report of the arrest of an ulcerative carcinoma of the bladder by the inactivation of that organ This situation of dependency by a seemingly-mature tumor on a particular hormone balance is not, to our knowledge, paralleled in the instance of bronchogenic carcinoma However, these instances prove that the complete autonomy once attributed to malignancy is unsupported by the present findings

More important to the study of lung cancer is the observation that, in certain organs, microscopically visible clusters of cells which have all the histologic criteria of malignancy can remain *in situ* for long periods of apparent inactivity, although classical tumors usually develop at these sites in time It would seem that malignancy is not

a consistently steady development and very early malignancies do not necessarily follow the pattern devised for larger growths.

It would be a mistake to assume a latent period for bronchogenic carcinoma merely by analogy with other types of malignancy. On the other hand we cannot assume that such a situation does not exist. In cytologic studies we have found some reason to suspect that there may be a distinctive early phase of the disease which is characterized by the production of an enormous number of free cancer cells without a proportionate development of the tumor body. A tumor at the carina of a patient which was so small that it was not found during the first two bronchoscopies was proven by cytologic studies to be exfoliating countless free cells into the bronchial secretions. Thus far there is not enough evidence to speak with assurance, but it is at least possible that bronchogenic carcinoma undergoes a stage of development shortly after its inception characterized by vigorous cell production in which these malignant cells are not organized into tumor body.

The case histories which we collected from nearby institutions did not lend themselves to analysis regarding a very important aspect of histopathology—the relation of cell type to typical development. However, in general a sufficient number of studies of this subject have been made to confirm the common clinical observations on the disease. Gebauer and Koletsky have each analyzed collections of case histories to this end.

Squamous cell carcinoma. It is apparent that squamous cell carcinoma has its origin approximately 70 to 80 per cent of the time in one of the primary branches of the bronchial tree at or very near a bifurcation, although in isolated instances it may originate in the neighborhood of the trachea. Presumably it begins in the layer of basal

cells in the bronchus and its growth is primarily extrabronchial, into the parenchyma, around a smaller bronchus

Squamous cell carcinoma usually interferes with the functioning of the affected lobe by constricting, rather than by filling, the bronchus In its intrabronchial development it seems especially liable to erosion, consequently, it may produce distinctive clinical symptoms early in its course The tumor body itself, in the parenchyma, is somewhat more likely to undergo necrosis and cavitation than other types of bronchogenic carcinoma, probably because of an inadequate blood supply

Although statistical findings have only a limited application in clinical practice, it is worth noting that squamous cell carcinoma is generally much slower to metastasize than other types Such metastasis, when it occurs is usually via the bloodstream, with perhaps a predilection for cerebral metastases The aversion of squamous cell carcinoma to the lymphatic system is oftentimes marked It is not unusual to find at autopsy that this growth has actually detoured around a lymph node On the other hand, it is ruthlessly invasive of non lymphatic contiguous structures, and often becomes inoperable by reason of its penetration into the pleura The so called "Pancoast superior sulcus tumor," with its early and painful extension into non-pulmonary structures, is usually a squamous cell tumor of an upper lobe

Adenocarcinoma. This form of malignancy generally begins farther out in the lung than does squamous cell carcinoma Gebauer found that 70 per cent of these growths originated in secondary branches of the tracheobronchial tree, and another 20 per cent in the smaller branch bronchi Much more of the tumor body is endobronchially located than is characteristic of the other pulmonary malignancies It frequently penetrates the bron

chial lumen early in its course and by this growth it may occlude the bronchus while still quite small The enlargement of the endobronchial growth is generally toward the trachea On rare occasions a small adenocarcinoma may seem to be entirely intra bronchial In most instances however the intrabronchial growth will be accompanied by the extension of the tumor into the parenchyma from which it is usually delimited rather sharply Roentgenologically or at autopsy an adenocarcinoma sometimes appears as two parts thinly joined through the point of origin

Adenocarcinomas are not particularly fast growing as malignancies go but they may metastasize widely quite early in their course Lymphatic spread is particularly notable such metastases may appear as a series of connected tumors at autopsy Not infrequently the carinal lymph node metastases exceed the original growth in size Blood stream metastases are also common

These malignancies also invade blood vessels more readily than any other pulmonary growth A squamous cell carcinoma is apt to produce blood streaked sputum because of its mucosal erosion adenocarcinomas may also produce such blood streaked sputum but one frequently encounters episodes of frank hemoptysis as the tumor invades small blood vessels Pulmonary hemorrhage may be the immediate cause of death if larger vessels are attacked

Undifferentiated carcinoma Over one half and perhaps three quarters of all round cell oat cell and spindle cell carcinomas originate in a main stem bronchus Most of the remainder begin in a secondary bronchus although they have been reported in a peripheral location This cell type would seem to have a predilection for the right lung and for upper lobes

Growth is predominantly extrabronchial as with squa

mous carcinoma but undifferentiated carcinoma has a notorious predilection for invasive growth into the mediastinum fixing and distorting the bronchial tree and choking the vital structures in that area The tumor is one of the most nonselective of common malignancies However it does not readily occlude the bronchus of origin and on occasion it may be seen to extend for long distances within the bronchial structures without penetrating the lumen Atelectasis is therefore uncommon

Although one encounters exceptional cases in general undifferentiated carcinoma may be safely asserted to be the most rapidly growing tumor of the bronchial tree and it runs the shortest course Its growth within the lung is usually along the bronchus of origin but it is also irregularly infiltrative into adjacent parenchyma and may extend into the pleura

Undifferentiated carcinoma like adenocarcinoma has a pronouced affinity for the lymphatic system It is sometimes seen to follow lymphatic channels in its spread and it also tends to metastasize widely through the lymph system Adjacent lymph nodes are almost always involved and secondary lymphatic involvement may be so extensive as to obliterate normal lymph node structure and over shadow, both roentgenologically and clinically the site of origin Lymph node metastasis may be more extensive in undifferentiated carcinoma than in adenocarcinoma we feel that the gross abdominal node and cervical node involvement is seen somewhat more frequently in the former

In addition undifferentiated carcinoma is very apt to metastasize via the blood stream In the series of cases reported by Koletsky almost half the patients with undifferentiated carcinoma were found at autopsy to have secondary growths in the liver and the adrenals with the pancreas providing the next most common site

THE SIGNIFICANCE OF PATHOLOGIC CLASSIFICATION

The correlation of cell type with clinical behavior is a very tentative procedure. It must be emphasized that we have no reason to expect that there will ever by any kind of dependable, one-to-one relationship between these two aspects of bronchogenic carcinoma. Our object is to determine the predilection of a particular morphologic type for a certain kind of clinical behavior. The results may prove to be of more service to the study of etiology than in clinical prognosis.

Furthermore, the information relating to this subject which has been reported so far is probably more than a few percentage points from the true situation. To repeat what was said at the beginning of this chapter, the confusion surrounding the subject arise from two causes: (1) Students are not in complete agreement as to proper classification, so that the same tumor might be differently described by competent pathologists, and (2) the pains taking autopsy studies necessary for correlation with clinical findings are few.

The difficulties involved are apparent when statistical studies are examined. The basic test for these studies is the percentage of each morphologic form in total incidence. There should be some kind of correlation between different studies on this basic question, there is not. In such studies, squamous cell carcinoma has been reported as comprising from 5 to 65 per cent of total incidence—a disheartening range. In our own study of 1070 autopsies, it was necessary to depend upon the written reports of pathologists (Figure 6). In this series about 40 per cent of the tumors which were classified were squamous cell carcinomas. It was apparent from these reports, however, that too frequently the pathologists' descriptions were based upon few sections. Furthermore, the percent-

age of tumors which were unclassifiable on the basis of these reports casts some doubt on the findings where classification was possible In view of these difficulties, it seems best to summarize some common obervations without pretending to a misleading exactness

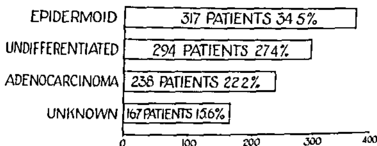


Figure 6 Distribution of cell type in 1 070 autopsied patients with bronchogenic Ca

One thing is clear, squamous cell carcinoma is the most common malignancy of the lung Our own figure of about 40 per cent probably represents its minimum incidence, it may comprise as high as 65 to 75 per cent of all primary tumors of the lung Squamous cell carcinoma is also primarily a disease of the male sex The proportion is perhaps 10 to 1 or higher The sex frequency of undifferentiated cell carcinoma is uncertain, since published reports on this subject vary widely It probably does not have the degree of male sex predilection that squamous cell carcinoma has, but it would seem to be more common in the male sex than in the female Adenocarcinoma on the other hand, is probably the most common form of lung tumor among females, who make up perhaps half of the total incidence of that cell type

There would also seem to be a considerable difference in the average age at which the three forms become manifest Squamous cell carcinoma is overwhelmingly a disease of the elderly, although rarely it may occur in children Adenocarcinoma shows a mean age of from 35 to

40 perhaps some 15 years less than the average age for squamous carcinoma Undifferentiated carcinoma shows a mean age range similar to that of adenocarcinoma Again conclusions must be tentative but it seems that adenocarcinoma and undifferentiated carcinoma together are the most common forms of lung malignancy below the age of forty but that over the age of 45 squamous cell carcinoma is by far the most prevalent It should be pointed out that where etiologic agents have been established for lung malignancy the malignancy is almost invariably epidermoid

ASSOCIATED PATHOLOGY

Most of the pulmonary pathology associated with bronchogenic carcinoma can be attributed directly or indirectly to bronchial obstruction Atelectasis is the most prominent secondary development in adenocarcinoma and epidermoid tumors The extent of such atelectasis will of course depend upon the location of the growth With adenocarcinoma the tendency of the intra bronchial portion of the tumor to move upward toward the hilus produces at times a condition in which the area of atelectasis is seen roentgenologically to enlarge gradually Squamous cell carcinoma usually produces atelectasis by constricting and eroding the bronchus exteriorly until it collapses Where a major bronchus is occluded the consequent massive atelectasis may produce compensatory emphysema contralaterally

Atelectasis is followed sooner or later by infection since bacteria can multiply without hindrance in the secretions which are backed up behind the obstruction In our experience the beginning of such an infectious phase is often acute and resembles a mild pneumonia in its symptomology After the acute episode passes the infection usually progresses into a chronic suppurative

condition resembling bronchiectasis Eventually the in fection may proceed to widespread necrosis and abscess formation Abscess and cavitation may also occur within the body of the tumor itself, especially if the growth is a low-grade squamous cell carcinoma Any abscess has of course, the possibility of rupturing into the pleura and producing an emphysema

Prior to the development of this process of atelectasis and infection, an intermediate process is sometimes seen roentgenologically As long as the occlusion of the bron chus by the tumor is somewhat less than complete, a oneway valve condition may develop, producing a tem porary emphysema in the parenchyma distal to the tumor body This is particularly apt to occur when the tumor is an adenocarcinoma

Even when a growth does not occlude a bronchus, some degree of infection is probably always a secondary development Erosion of the growth through the lumen of the bronchus produces a condition favoring infection Very often there is also a certain amount of infection in the parenchyma surrounding the tumor body exterior to the bronchus Even when atelectasis is not a factor, this parenchymal infection may at times be considerable The extensive areas of infection frequently observed in un differentiated carcinoma, as determined by roentgenologic studies before and after a course of antibiotics, might suggest that there is some correlation between the amount of secondary infection (not dependent upon atelectasis) and the degree of invasiveness the tumor body manifests

Out side of associated infection, the secondary pathol ogy attendent upon a primary lung tumor is atypical and bizarre Location of the tumor body is of course, critical to future developments There seems to be some relation ship between metastatic sites and their frequency and the morphologic type of the primary growth, but it is by no

means a clear-cut relationship The table below listing these sites merely emphasizes the many possibilities

In the experience of the author, in many cases of inoperable bronchogenic carcinoma, life expectancy appears to depend upon factors in the relationship between the new growth and the host that are entirely unknown Some patients tolerate an enormous amount of neoplastic tissue without an excessive loss of strength, and survive until there is interference with a vital function Other patients respond very strongly to comparatively confined growths, and death seems to come about by an unknown form of toxicity Clinically, one frequently observes cases of early malignancy in which fatigue, loss of weight and other general symptoms are out of all proportion to any conceivable direct effect of the tumor

Clinical Features | 3

AT LEAST a majority of all patients with bronchogenic carcinoma are theoretically still amenable to surgery after the onset of symptoms. Nevertheless, our actual operative rate does not approach 10 per cent. The difference between the theoretical rate of cure and the actual achievement is the measure of our failure to diagnose the disease promptly. In the last 15 years—the period in which thoracic surgery has become a feasible and practical procedure—there has been no measurable improvement in diagnosis at all. In our study, the interval between the onset of symptoms and hospital entry has remained approximately the same, averaging about 22.5 weeks. Lindskog, Overholt, and Schmidt have described similar findings in recent studies. There has been a great improvement in diagnostic facilities and techniques during this period, but the application of these techniques has been ineffective.

There are two distinct intervals involved in this delay. There is inevitably a period between onset of symptoms and the appearance of the patient before the physician. There is a further interval before a proper diagnosis is made. The reduction of the first interval, between the onset of symptoms and the first medical examination depends upon education of the public. The layman must be trained to have a serious regard for minor chest symptoms

(without educating him to hypochondria) and preferably, to periodic physical examinations To date we have depended upon carefully organized campaigns by cancer control groups to accomplish this indoctrination So far as bronchogenic carcinoma is concerned, these campaigns have probably been without demonstrable effect The patient continues to procrastinate and neglect chest symptoms Such campaigns must be continued, since they are our only means of reaching a large proportion of the population, but we cannot expect that they will be of much benefit except over a long period of time On the other hand, it seems probable that the personal influence of the individual physician, exerted over the widest possible area, would be able to effect a substantial improvement in the percentage of bronchogenic carcinomas subject to excision when diagnosis is made, and that his influence would operate much more quickly and directly

The reduction of the second interval, between presentation and diagnosis, is one of the primary problems of contemporary medicine (Figure 7) It is often assumed, however, that the solution is again one of simple education, that we can bring about early diagnosis simply by stimulating the medical profession to an increased awareness of the disease This is evidently not true The clinical aspects of bronchogenic carcinoma have been the subject of writing and discussion for many years without concrete effect It must be recognized that the problem is one of complexity For every patient who presents himself to the physician with cough, moderate wheeze, some malaise or dyspnea, vague chest pains—that is, with the early symptoms of bronchogenic carcinoma—there are hundreds who present themselves with a similar group of complaints which can be traced to minor respiratory infection or to no detectable organic difficulty Further, this large group of patients who seek medical attention chiefly for

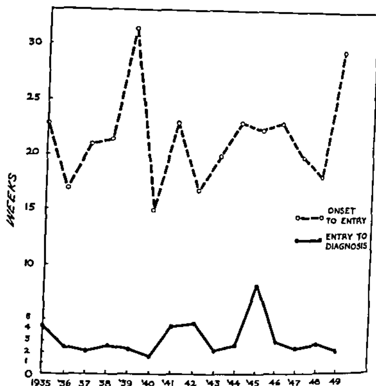


Figure 7 Time interval between onset of symptoms and hospital entry (interrupted line) and between hospital entry and time of diagnosis (solid line) from 1935 to 1949

reassurance is drawn in large measure from the same age group in which carcinoma is most apt to occur That the physician is reluctant to advise an extensive course of roentgenologic and other diagnostic studies for the major ity of his patients is understandable, and there is little to be accomplished by insisting upon the absolute signifi cance of minor symptoms

An increased awareness of the problem is of course necessary Every patient with minor chest complaints not immediately traceable to a known cause must be con

sidered, briefly at least, potentially carcinomatous But the question asked in such instances must be rephrased The question is not, "Are these the symptoms of bronchogenic carcinoma?" but, "Could a malignant process in the bronchus conceivably give rise to these appearances?" Further, it must be recognized that modern diagnostic techniques cannot, in this situation, replace traditional arts The thorough physical examination is a necessity, and symptoms must be evaluated in terms of a carefully taken history The physician's insight into the patient's problems must in many instances continue to determine his attitude toward the patient's symptoms

The difficulties in the diagnosis of bronchogenic carcinoma arise from the fact that there is not, even in a broad sense, a symptom complex which can be regarded as typical of the disease The primary pathology has its origin in an area in which much silent growth is possible As a consequence, most symptoms and signs are more or less secondary in nature, and their relationship to the tumor is eccentric This applies to respiratory symptoms, as well as to symptoms of a systemic nature and to those of extension or metastasis (Figure 8)

Respiratory symptoms Interest naturally focuses on the common respiratory symptoms, since they do not preclude operability However, such symptoms are not invariably found in bronchogenic carcinoma In our series, approximately 15 per cent of the 1,070 patients did not have, upon entry into the hospital, distinct bronchial symptoms The symptoms which led these patients to seek medical attention were those due to metastasis Furthermore, a substantial proportion of the remaining 85 per cent had complaints that were predominantly those of metastasis minor chest symptoms were discovered only incidentally when the patients were examined This group of patients, which probably comprises between 25 and 35

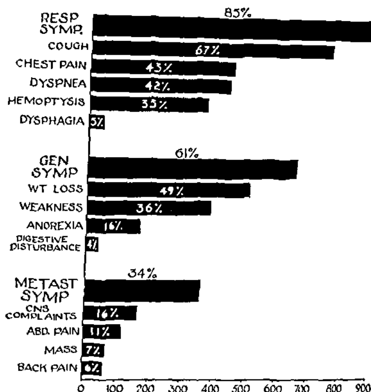


Figure 8 Symptomatology in 1 036 autopsied patients with bronchogenic carcinoma

per cent of the total incidence of bronchogenic carcinoma, are from the beginning, hopeless, so long as we must de pend upon surgery

Cough and sputum. In our s… ive cough, attributable to the pulmonary p… found in 67 per cent of al… (see Fi… is comp ble with most p… that there was … ch… considerably … r cen… chogenic carcir… a

nificant degree of intrabronchial growth will almost invariably produce cough Such a symptom may be the earliest to appear, and may persist throughout the course of the disease

The tumor, even when quite small, acts as a foreign body within the bronchus of origin Unless the growth is peripheral, a cough will develop which represents the natural effort of the protective mechanism to expel the obstruction Such a cough is frequently distinguished from the chronic "hack" which is characteristic of the present-day adult population by a distinctly paroxysmal character When it first appears it is customarily ignored, and is most apt to be noted in retrospect

Even a small intrabronchial tumor will obstruct the drainage of bronchial secretions If the tumor is peripheral cough may be productive from its first appearance Initially, the sputum raised is often described as gray and mucoid Very shortly after secretions begin to collect, however some degree of infection is likely to develop It is our observation that the development of an infection is apt to be initiated by a mildly acute inflammatory process, which the patient describes in retrospect as "flu"

Perhaps the most diagnostic early symptom of bronchogenic carcinoma is a productive cough which is abnormally persistent We have seen many patients who first came to our attention because of an acute respiratory infection which failed to clear after the initial episode At other times malignancy will be suggested by remission and recurrence a series of "pneumonias" Many more cases of bronchogenic carcinoma would be operable at diagnosis if time were not lost with repeated courses of antibiotic therapy in these instances

With the development of infection the sputum becomes mucopurulent Unless the progress of the infection is impeded by the use of chemotherapy, such sputum will

become frankly purulent in time and it will usually be copious If the tumor progresses to bronchial obstruction cough and sputum may disappear completely for a time but case histories suggest that there are frequent periods of temporary patency when a bronchus is occluded by tumor in which purulent sputum is raised copiously

Chest pain In our series chest pain was found to be the second most common respiratory symptom occurring in 43 per cent of 1 070 patients Ariel and his co workers in a series of 1 009 patients found this chest pain to be the symptom which led the patient to seek medical attention in 276 instances it was the most frequent presenting symptom in their series

Frequently one sees the pain accompanying bronchogenic carcinoma described as intense This probably reflects the advanced stage at which the disease commonly is diagnosed In our own practice we have noticed that in the earlier stages of the disease there is frequently chest pain but it is not severe The majority of our patients who have reported such a symptom have described it in moderate terms as an annoyance rather than a major discomfort It was most frequently described as a persistent aching unrelated to respiratory movement although not especially severe it was so notably persistent as to be oppressive This type of pain does not necessarily suggest inoperable extension it appears to be due to local compression of the bronchus with consequent ulceration and bronchial spasm It may also result from invasion of pulmonary blood vessels

There may be at some stage in the development of the disease a typical pleuritic pain for a short period This may persist until a pleural effusion develops Such pain is not necessarily indicative of pleural involvement

Severe chest pain frequently occurs in advanced stages of the disease The patient describes it as sharp and knife

like and the physician finds it difficult to alleviate Such an occurrence generally suggests extra pulmonary involvement either of the pleura the chest wall or the mediastinum Mediastinal involvement is suggested by sharp pain referred to the back *We have also observed a radicular type of pain which autopsy studies suggested was the result of nerve root involvement in the posterior mediastinum*

In a consideration of the clinical aspects of bronchogenic carcinoma it is important to remember that some kind of chest pain will be found almost half of the time and that such pain does not necessarily indicate that the growth is inoperable It is less important to attempt a classification of the forms that such chest pain can take

Dyspnea In our study we found dyspnea to be as common a symptom of bronchogenic carcinoma as chest pain This condition is due to inadequate oxygenation of the blood and suggests non functioning lung tissue In general this symptom was neither prominent nor severe At least one third of the normal lung capacity is reserve and the body is consequently able to tolerate a more or less massive collapse of lung tissue if the process is gradual enough to permit adjustment However there is no consistent correlation between the degree of dyspnea and the amount of lung tissue involved We have observed a number of patients in whom dyspnea was present even though the malignant growth was small and uncomplicated It is probable that the development of dyspnea is more complicated than our present understanding of the condition takes into account

Occasionally a severe attack of dyspnea develops in conjunction with bronchogenic carcinoma Such a symptom implies that a large amount of tissue has been withdrawn rather suddenly from the total vital capacity of the lung This may come about because of the development

of a massive pleural effusion, or it may herald the onset of lobar pneumonia Where severe dyspnea develops with out evidence of pneumonia or pleural effusion it is pre sumed that an extra bronchial growth has constricted a major bronchus

Hemoptysis. This is another symptom from which un warranted conclusions concerning operability are some times drawn It may appear as occasional expectoration of small amounts of bright red blood frank hemorrhage, or blood-streaked sputum The last type of hemoptysis is by far the most common It is occasioned by ulceration and infection of the bronchial mucosa or the intrabron chial portion of the tumor It is a common finding in squa mous cell carcinoma, it is much less common in the other types of bronchogenic carcinoma, which do not erode the mucosa It may be present at all stages of the squamous cell carcinoma, and it is not infrequently the presenting symptom This tendency is partially responsible for the more favorable prognosis of this type of tumor, bloody sputum is not likely to be neglected for long and there is a greater chance for early diagnosis

Hemoptysis occurred in 35 per cent of our patients and at least three fourths of the time it was reported as blood-streaked sputum When pure blood is expectorated it suggests an undifferentiated carcinoma or, even more likely an adenocarcinoma Squamous cell carcinoma has a marked aversion to blood vessels, the other types do not

General symptoms. The relationship of non specific systemic findings to bronchogenic carcinoma is not always clear Most commonly observed are weight loss weak ness, anorexia chronic fatigue and noctridosis, they can be roughly divided into symptoms of sepsis and loss of strength These are, of course, characteristic of the ad vanced stages of the disease on the other hand, they are not in themselves evidence for any such conclusion

Fever and sepsis The interest in general symptoms is due in part to the growing realization that careful attention to such developments in patients over 40 can contribute to early diagnosis of bronchogenic carcinoma It is more and more commonly recognized that some lung infection is frequently an early side-effect of bronchogenic carcinoma In many instances as has been mentioned fever and sepsis have an acute onset Fried found that 73 per cent of his series of lung cancer patients were diagnosed during or following an acute respiratory infection Of course there may be no acute episode initiating such an infection a lung segment blocked off from the trachea is susceptible to pathogens of a very low grade of activity and the beginning of an infection may be insidious In either instance cancer is suggested rather than the reverse Patients with lung cancer will almost always have some degree of fever at least intermittently Other evidence of sepsis is variable Night sweats occur but not as frequently as in patients with tuberculosis

Loss of strength Weakness loss of weight anorexia and chronic fatigue are characteristic findings in advanced states of bronchogenic carcinoma and the systemic imbalance that they represent may be directly responsible for the death of the patient However they can occur very early in the course of the disease although they are not so pronounced when the malignancy is pulmonary as when it is gastric In many instances they seem to be directly traceable to secondary suppurative processes We have been especially impressed by numerous instances however where such did not appear to be the case We have found marked loss of weight in instances where the secondary infection was mild metastases absent and the tumor body small Such loss of weight is frequently accompanied by a lassitude which is also out of all proportion to objective findings We believe that such symptoms

accompanied by moderate cough or any other slight respiratory sign, should strongly imply bronchogenic carcinoma. In such cases, malignancy must be ruled out before any other diagnosis can be made with assurance.

Metastatic findings. There remains a rather large group of patients in which the first serious manifestations of a disease process are due to metastasis. In our study, 34 per cent of the patients first sought medical attention because of symptoms which were due wholly or in part to metastatic lesions. It will be noted from the figure that many of these cases represented mediastinal involvement.

A tabulation of these findings merely emphasizes the infinite variety of metastatic sites possible and is without much profit (Table I). A thorough physical examination and a detailed case history will frequently uncover minor

TABLE I

SITES OF MALIGNANT EXTENSION OR METASTASES
(1070 Autopsied Patients with Bronchogenic Carcinoma)

Site	*All Types* Number	*All Types* Per cent	*Squamous* Per cent	*Undiff* Per cent	*Adeno* Per cent
Metastases limited to Hilar L. N.	98	9.2	12.6	6.5	4.6
Hilar L. N.	790	73.8	58.2	94.5	64.3
Brain *	201 *	50.4	37.3	55.6	61.9
Liver	479	44.8	27.2	65.0	38.2
Adrenal	428	40.0	29.1	54.8	35.4
Pleura	308	28.8	22.0	38.7	28.1
Kidney	286	26.7	22.0	36.5	20.7
Heart	214	20.0	17.0	21.2	16.7
Abdominal L. N.	202	18.9	16.6	25.1	11.9
Opposite lung	199	18.6	14.7	16.3	23.5
Pancreas	120	11.2	5.9	18.3	8.4
Spleen	87	8.1	5.9	12.9	7.1
Cervical L. N.	61	5.7	5.5	8.8	6.3
Intestine	60	5.6	3.0	7.0	4.8
Skin and subcutaneous tissue	41	3.8	2.4	3.1	8.4
No metastases	103	9.6	13.5	4.4	7.1

* The brain was examined in only 399 cases.

signs and symptoms that will indicate coexistent disease sites Perhaps it should be pointed out that just as debility by itself does not prove a patient inoperable, so physical vigor does not prove the reverse Among our patients who first sought medical attention for symptoms arising from metastases, many appeared to be in excellent physical condition, and did not consider themselves seriously ill Such patients, however, usually failed with alarming rapidity after the onset of symptoms

PHYSICAL EXAMINATION

The patient is very apt, then, to present himself for medical attention with one or more complaints of a rather low order of severity In a large majority of cases there will be at least one complaint which is respiratory (Table II) Although it may be impracticable to hospitalize such

TABLE II

PHYSICAL FINDINGS

(1070 Autopsied Patients with Bronchogenic Carcinoma)

Finding	No.	%
Evidence suggestive of pulmonary disease	780	73%
Pleural Effusion	353	33%
Gross metastatic lesions	482	45%
Significant L N enlargement	182	17%
Abdominal mass	150	14%
Skin nodule bone mass brain tumor etc	149	14%
Clubbing	96	9%
Horner's Syndrome	21	2%

patients for diagnosis, a thorough physical examination is certainly obligatory, and in most instances of lung cancer there will be suggestive findings if the nature of the malignant lesion is kept in mind

Wheeze. Ordinarily, the first evidence of a disease process which is detectable by ordinary physical examination is a wheeze However, a wheeze due to a new growth cannot readily be distinguished from the miscellaneous

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Hilar L N	790	73 8	58 2	94 5	64 3
Brain *	201 *	50 4	37 3	55 6	61 9
Liver	479	44 8	27 2	65 0	38 2
Adrenal	428	40 0	29 1	54 8	35 4
Pleura	308	28 8	22 0	38 7	28 1
Kidney	286	26 7	22 0	36 5	20 7
Heart	214	20 0	17 0	21 2	16 7
Abdominal L N	202	18 9	16 6	25 1	11 9
Opposite lung	199	18 6	14 7	16 3	23 5
Pancreas	120	11 2	5 9	18 3	8 4
Spleen	87	8 1	5 9	12 9	7 1
Cervical L N	61	5 7	5 5	8 8	6 3
Intestine	60	5 6	3 0	7 0	4 8
Skin and subcutaneous tissue	41	3 8	2 4	3 1	8 4
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collection of sounds which are produced in the normal bronchus by loose mucous It may be noted to be rather dry and brassy, and the patient may observe that it is chronic When possible it is sometimes helpful if the patient is given one half or one grain of codeine orally an hour before arising and examined immediately upon arising The codeine suppresses the cough reflex and often results in the accumulation of sputum at the point of obstruction When the patient is examined the wheeze will then be prominent and more readily localized A persistent unilateral wheeze in a patient over 40 is almost pathognomonic of serious bronchial obstruction

The length of time that a partial obstruction exists in the bronchus so as to cause wheezing probably varies widely On the basis of the number of times that the condition is recorded clinically it would seem to be a short period Consequently such a wheeze is most apt to appear when the history is taken When there has been an episode of acute pneumonia the patient will sometimes report a period of wheezing preceding the infection

Emphysema The wheezing stage in the development of bronchogenic carcinoma is not infrequently followed by a yet briefer stage of emphysema The degree of emphysema depends primarily upon the location of the tumor Because bronchogenic carcinoma is characteristically located in primary and secondary branches of the bronchial tree emphysema may be of great extent and detectable by careful physical examination A tympanitic percussion note may be a typical finding but diminished or absent breath sounds over the affected area are more easily detected Emphysema is suggested by unilaterally diminished respiratory movements In any case it is a fleeting appearance and emphysema as a result of bronchial carcinoma is not commonly seen clinically

Atelectasis The chronic condition accompanying

most cases of bronchogenic carcinoma is atelectasis which follows complete stenosis of the bronchus It is very difficult to distinguish this condition from an inflammatory process by a physical examination but in either case a roentgen ray examination is mandatory and the segmental distribution of a shadow due to atelectasis will usually permit accurate differentiation

The only condition which is likely to obscure an atelectatic lung segment is pleural fluid This is readily demonstrated in a physical examination if it is extensive Such a finding suggests a serious pulmonary abnormality and demands further diagnostic studies We would emphasize again that if such fluid is withdrawn and found to be clear and free of tumor cells it does not prove that the primary pathology is non-cancerous Moderate amounts of clear fluid are not infrequently found in the pleura due to lymphatic blockage or to lung infections secondary to malignancy

Clubbing of the extremities Clubbing of the extremities is not of course a dependable finding in bronchogenic carcinoma but when observed it may be very helpful in diagnosis This condition which seems to result from a deficiency in the aeration of the blood may accompany any chronic lung infection However when the primary pathology is infectious clubbing develops only after a considerable period of time On the other hand it may develop very rapidly in the presence of a lung cancer in a matter of weeks Whenever such clubbing is observed and there is not a long history of respiratory or circulatory disease bronchogenic carcinoma should be suspected Fried found clubbed fingers in 30 per cent of his patients with early bronchogenic carcinoma it occurred in our series almost 10 per cent of the time

Tracheal deviation Some tracheal deviation in the presence of atelectasis will usually be detectable on physi

cal examination Even when such atelectasis is not present, the position of the trachea should be determined It has been, in our experience, the most concrete physical indication of pulmonary pathology in a few instances where the malignancy was a predominantly extra bronchial, undifferentiated carcinoma Such growths rather frequently displace the trachea to an appreciable extent without other prominent physical findings

Metastasis. The search for metastatic findings is apt to seem a somewhat academic procedure in preliminary physical examination However, we believe that a physical examination should be routinely a complete examination, and that it must include the whole body When there is suspicion of lung pathology in a patient over 40, this examination should be especially concerned with the possibility of nerve involvement, particularly those nerves passing through the mediastinum Superficial lymph nodes should be carefully palpated in the presence of any disease process Such a thorough physical examination is still the basic procedure in the practice of medicine Most of the scientific procedures which have been developed and which have had an unfortunate tendency to replace the physical examination depend upon the physical examination or the history to indicate the kind of information required

And it is to this purpose that all of the preliminary procedures of history taking and physical examination should be directed Even a presumptive diagnosis is generally impossible upon the basis of such findings, but if they are carefully analyzed they can ordinarily be trusted to suggest the possibility of serious pulmonary pathology requiring further study Upon the basis of such findings the physician must make his first important decision, he must decide whether or not further studies are required

Roentgenology | 4

When upon the basis of a patient s symptoms and physical findings lung malignancy is considered possible a diagnosis must be made or ruled out as quickly as possible by means of specialized diagnostic techniques the chief of which is roentgenology The pleomorphic characteristics of this disease however make roentgenologic findings difficult to evaluate There are to be sure certain "classic" x ray appearances in bronchogenic carcinoma but these are neither the most common nor are they the appearances offering the best prognosis Typically bronchogenic carcinoma masquerades as something else and the real nature of the condition will only be suspected by someone with long experience As a consequence effec

of the disease should be of only minor interest to the clinician He after all must finally make the diagnosis and this requires that he understand the radiologist s conclusions in the light of the latter s problems There must be mutual understanding and close cooperation between the two the radiologist will function most effectively if he is able to interpret and evaluate his findings with full knowledge of all clinical data in the light of basic pathology The ideal situation which is more and more

being realized in practice, is one in which the clinician and the radiologist consult frequently, and where the clinician is routinely present at roentgenologic examinations

We shall not attempt, then, to describe exhaustively the means for a roentgenologic diagnosis of bronchogenic carcinoma, these require the techniques of a specialist and cannot be covered in a chapter, or in a book Instead we shall try to present the knowledge of roentgenology which is required by the clinician for effective cooperation with the radiologist We shall describe basic appearances necessarily oversimplifying and try to indicate the findings which are most apt to be misleading, if clinical material is not given full consideration Lastly, we shall suggest briefly the range of supplementary techniques by which an obscure roentgenologic appearance can sometimes be clarified

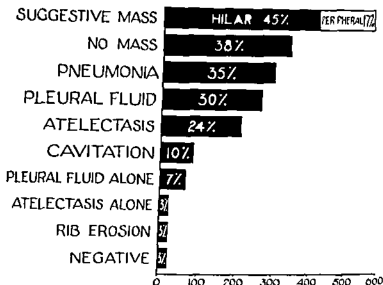
Fluoroscopy. First, it is perhaps well to recognize that many physicians operate their own fluoroscopes routinely for cardiac and other examinations, and that in many instances the first roentgenologic study of a patient with bronchogenic carcinoma will be fluoroscopic examination in the physician's office The danger is that this procedure will sometimes replace a complete roentgenologic study If, however, it is regarded as a supplement to the physical examination, and if it is thorough, it can be of service in establishing the existence of a pathologic process, and the necessity for a complete roentgenologic study In our own practice, we have found that the usefulness of fluoroscopy depends in great part upon there being a definite procedure which is routinely followed in the examination Such a routine prevents minor abnormalities from being overlooked, shortens the examination time, and minimizes exposure

The examination should begin with the patient facing

the projector The examiner should first note the general configuration of the chest the size shape and position of the cardiac silhouette and then closely observe the mediastinal shadow Tracheal deviation is looked for Each cardiophrenic and costophrenic angle of the diaphragm should be carefully inspected for signs of fluid formation After a general inspection of the thoracic cage with wide open shutters they should be coned down for a detailed inspection A methodical examination of the whole area should then be made working from top to bottom We customarily use a lateral slit in this detailed survey because minor abnormalities are often best detected by a comparison of one side of the chest with the other

Fluoroscopy has one real advantage over roentgenray films in that it permits observation of lung movement Even a pathological process of limited extent very frequently disturbs the functional relationship of the two lungs or of segments of the same lung Such a disturbance can be detected in two ways by fluoroscopy In the first place the movement of the two leaves of the diaphragm should be carefully compared at full inspiration at full expiration and during normal respiration Any disparity between them in extreme positions or any time lag observed suggests lung pathology It is also possible to compare the different segments of the same lung with each other This is done with a vertical slit By observing the position of the lung markings at full inspiration and expiration it is sometimes possible to detect an unequal expansion among the segments which usually suggests a limited area of emphysema due to partial bronchial obstruction

In any event fluoroscopy should not be regarded as anything more than a confirmation of the presence of an abnormality and a guide to further roentgenologic



F gi re 9 \ ray find ngs — 889 pat ents

studies Such further studies should routinely include lateral views as well as standard posterior anterior projections If the formal roentgenologic examination is guided by further fluoroscopy oblique views may be suggested

There have been many attempts to devise and illustrate certain classical x ray appearances found in bronchogenic carcinoma a discussion of the subject in fact requires that such standard appearances be presumed It must be remembered however that the distinct appearances described in literature are very apt to be inextricably confused in the particular instance In our study of autopsy reports of 1 070 patients with bronchogenic carcinoma there were 889 for whom adequate x ray reports or the x ray films themselves were available A tabulation of findings (Figure 9) indicates that a tumor body was visible almost two thirds of the time However in a majority of these instances as the rest of the table sug

gests, there were other findings that tended to obscure the basic shadow In order to discuss the subject at all, it is necessary to discuss separate appearances It must be remembered, however, that separation of shadow from shadow is at times a difficult procedure (Figures 10, 11 12, 13)

For convenience, we can classify roentgenologic appearances in bronchogenic carcinoma into three large groups (1) those instances in which the tumor body itself is the chief roentgenologic feature (2) those instances in which the predominant appearance is that of bronchial obstruction and (3) those instances in which the appearance is overwhelmingly of lung infection We shall point out from time to time the correlation of cell type to roentgenologic appearance when in our experience it is particularly significant, but we shall not make a point of establishing such a correlation in each instance We believe that the kind of correlation that Gebauer and Koletsky have attempted to establish between predominant cell type and clinical and roentgenological appearances really exist but its interest and significance are etiological and not clinical The problem is to arrive promptly and accurately at a diagnosis of malignant neoplasm in clinical practice cell type is of little application at the present time

Parenchymal tumors As has been pointed out elsewhere between 5 and 15 per cent of all bronchial malignancies arise in lesser branches of the bronchial tree The tumor body itself in these instances is apt to be the most prominent roentgenologic indication of pathology because obstruction of the airways is limited Such growths are often quite spherical in shape with deceptively sharp contours Until these peripheral tumors become inoperable by reason of local extension into the chest wall or by metastasis, they are customarily quite silent Often





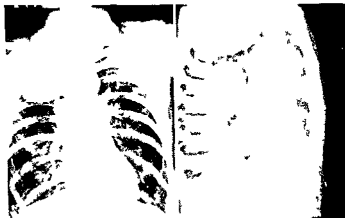
1a 1b





2a 2b

Figure 10



3a 3b



4a 4b

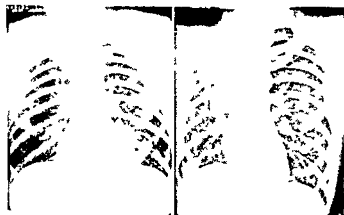
F g re 11



Figure 12



9 10



11 12

Figure 13

times the patient with such a tumor will first seek medical attention for symptoms due to metastatic growths, or they may be discovered in routine examinations Roentgenologically, they are readily mistaken for tuberculomas cysts, or benign growths Because of their silence, there has been a tendency in the past to treat such peripheral shadows as benign curiosities, until growth or metastases appear

The above description does not exhaust the roentgenologic appearances possible to peripheral tumors While there are no structures in the parenchyma of the lung which are able to distort new growths from sphericity by resistance, the predilection that certain of these tumors have for lymphatic tissue may completely alter their outline Such growths upon x ray examination are patchy and irregular in appearance, and may seem to be typical infections If such a growth occurs in an upper lobe, tuberculosis suggests itself, if in a lower lobe, pneumonitis, or infarct These tumors may be seen to vary somewhat between examinations, due to coexistent infection but the basic shadow somewhat is that of tumor tissue, which will not regress under chemotherapy

Hilar lesions Hilar type carcinoma is usually defined as malignancy arising near the midline of the thoracic cage which does not markedly occlude bronchi Such tumors are almost always anaplastic carcinomas these growths may involve bronchial structures extensively without causing obstruction At times the predominant appearance is of a roughly lobular growth in the parenchyma adjacent to the bronchus of origin More often these tumors follow the bronchi or the lymph channels in their extension The roentgenologic appearance may vary from that of a solid somewhat irregular shadow with blurred edges, to a more or less prominent exaggeration of lung markings

In our experience hilar lesions are the least confusing of all lung malignancies to roentgenologic diagnosis. However, when a solid, more or less lobulated shadow in this region is the chief roentgenologic finding, both sarcoidosis and Hodgkin's disease must be considered in the differential diagnosis. Also early growths of the highly invasive type, when they occur in this form, may be mistaken for bronchial infections. In some instances we have observed such an x-ray finding interpreted as consistent with tuberculosis.

BRONCHIAL BLOCK

Whenever a new growth is pronouncedly intrabronchial and occurs in a major branch of the bronchial tree, secondary conditions inevitably obscure the tumor body to a considerable degree. For convenience these secondary appearances can be divided into those which are predominantly infectious and those in which the most prominent evidence of abnormality is an uncomplicated bronchial block (Figure 14). In practice, of course, there is almost always some degree of overlapping. One seldom sees a roentgenologic film of bronchial obstruction without some evidence of coexistent infection, nor, except in far advanced cases of the disease, does a shadow of infectious origin commonly obliterate entirely the shadow of tumor tissue or atelectasis.

Emphysema. Westermark, in an interesting study, has

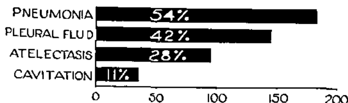


Figure 14. X-ray findings in 338 patients with No Mass on x-ray

distinguished three phases of lung pathology secondary to partial bronchial obstruction The first phase is that of hyperemia due to a decreased intra alveolar pressure the result roentgenologically is a faint darkening of the affected area The second phase is initiated by the devel opment of a one way valve condition which permits inspiration but inhibits expiration This is seen roentgeno logically as an area of increased radio penetration and lightness The third phase is complete block with an overly distended lung and emphysema beyond the occlu sion This description is physiologically convincing but its usefulness in clinical practice is doubtful It is well to keep this progression of events in mind but the sequence will seldom be observed We have not seen the first phase Westermark describes and have seldom been able to dis tinguish between the later phases of development

The significance of emphysema as a symptom of bron chogenic carcinoma has been discounted It is probable that an emphysematous phase does occur very often in lung malignancy but it is usually quite transient There is no way of determining the number of patients with bronchogenic carcinoma who have detectable emphysema when they are first fluoroscoped our experience would suggest that the number is small This group is important however emphysema offers at least the presumption that the tumor is in a relatively early stage of development and that the chances for successful surgery are good

There is a tendency at the present time to over empha size the increased lung transparency characteristic of an emphysematous area Such a change in radiolucency may be very difficult to detect with assurance unless it is ex tensive The usefulness of this appearance is further di minished because some degree of chronic emphysema without other lung pathology is common among older males

Atelectasis Uncomplicated atelectasis seldom offers diagnostic difficulty on roentgenologic examination The affected lung segment is markedly denser than normal the trachea heart and mediastinum are retracted toward the abnormal side, and the diaphragm is elevated If the affected segment is the left lower lobe, the primary appearance, that of the atelectatic lung tissue, may be more or less hidden in the heart shadow, but the consequent displacement of thoracic structures should prevent confusion Lateral x ray studies are of particular value in this situation

However, atelectatic appearances will usually be to some extent complicated by infection Experimental studies suggest that atelectasis implies infection since unless there are inflammatory changes in the alveolar walls there will be sufficient gas exchange between the alveoli of one segment and those of adjacent segments to prevent segmental collapse In the earlier stages of atelectasis such infection is usually low grade, and confined to the particular segment, with time, however, this infection will extend to adjacent tissue, and the segmental character of the lesion may be partially obscured

Although this condition may occur in conjunction with minor infectious processes this situation is uncommon When this characteristic appearance is seen roentgenologically the underlying pathology should be investigated without delay Most atelectasis in adults is due to new growths benign or malignant, although inflammatory disease and foreign bodies must be considered in the differential diagnosis

SECONDARY INFECTIONS

It is impossible to describe exhaustively the appearances possible to an infection secondary to bronchogenic carcinoma, since the course of such an infection will de

pend upon a multitude of more or less fortuitous factors It is usually impossible, by ordinary roentgen ray films, to distinguish between a primary infection and one secondary to malignancy However, by careful analysis it may be possible, in secondary infections, to detect features which will suggest an underlying pathological process

A tumor body is most apt to be completely masked by a secondary pneumonia, either chronic or acute This development frequently occurs while the neoplasm is still quite small, it may occur before there is complete occlusion of the bronchus of origin In such instances, the pneumonia may seem to clear completely following a course of chemotherapy However, it inevitably recurs Ordinary roentgenologic techniques are inadequate for the diagnosis of the primary condition

Something of the same situation exists so far as bronchiectasis is concerned In perhaps 25 per cent of all bronchogenic carcinoma, a diagnosis of bronchiectasis is listed as a possibility on the basis of roentgenologic studies Because the shadow of infection in bronchiectasis is apt to be less dense, and less compact than a pneumonia shadow there is sometimes direct evidence of the tumor body to be seen Over exposed hard shots are very useful when there is the possibility of a tumor induced bronchiectasis

Roentgenologic films of a lung cavity due to central necrosis of a malignancy will be diagnostic in many instances The cavity with thick, irregular walls suggestive of an invasive process, with or without a fluid level is the most common appearance However, this finding cannot be depended upon A tuberculous cavity may have the appearance of solid growth with central necrosis of limited extent a carcinoma may have walls so thin that the total appearance is that of an infected cyst

Up to one half of all bronchogenic carcinomas have

infection as the most prominent appearance when first x rayed In the study of roentgen diagnosis by Cooper and Kroll about a third of such cases did not suggest bronchogenic carcinoma to the roentgenologist It is obvious that in this situation above all others the cooperation of the clinician and the roentgenologist is indispensable Although the symptoms of sepsis and purulent sputum containing micro organisms will tend to confirm the roentgenologic findings of infection there is usually at least in retrospect facts which make such a diagnosis doubtful Anything in the roentgenologic findings clinical course or history which is atypical makes it mandatory that malignancy be ruled out by further studies

Perhaps the most common and frequently ignored indication of malignancy is the intractability of the lesion to routine chemotherapy This intractability usually manifests itself in a failure of the lung fields to clear as symptoms disappear by repeated attacks of pneumonia or by an inadequate response of symptoms to drugs The most useful procedure in avoiding unnecessary delay in arriving at the proper diagnosis of malignancy is the repeated use of the roentgenray all instances of pneumonia bronchiectasis and other major lung infections should be followed until the lung fields are clear

The history of the patient should also be correlated with roentgenologic findings Many studies of case histories in the pre chemotherapeutic era confirm the common observation that a lung abscess or a local lung infection was preceded by a history of an operation under anesthesia an infected wound of some sort marked oral sepsis, or dental extraction A diagnosis of primary lung abscess or primary pneumonitis should not be made without such a history until the possibility of carcinoma has been thoroughly explored

Something of the same situation exists so far as bron

chiectasis is concerned Though it is not invariably the case this disease usually develops in the first three decades of life Therefore findings of bronchiectasis in a patient over forty without a clear history of chronic lung infection extending over a period of years is in itself an indication of carcinoma rather than otherwise In such instances the burden of proof must remain with those who would arrive at a diagnosis of non malignancy

Most effective use of roentgenology then depends upon the correlation of roentgenologic findings with every available bit of information which in turn depends upon the cooperation of the roentgenologist and the clinician At times the pre operative diagnosis must depend upon these two sources of information alone In most instances however clinical and standard roentgenologic findings will be largely a guide to further studies Roentgenology itself can provide additional information by the use of supplementary techniques the chief of which are bronchography tomography and angiocardiography

SUPPLEMENTARY ROENTGENOLOGIC TECHNIQUES

Bronchography The most useful supplementary roentgenologic technique for the diagnosis of bronchogenic carcinoma is bronchography There is perhaps still some suspicion of this procedure on the theory that the iodized oil mildly irritates bronchial surfaces and leads to extension of an infection In our judgment however chemotherapy has almost eliminated this risk and the information that can sometimes be obtained by this procedure is worth the slight disability Many types of obstruction in the bronchi are readily detected by this technique and roentgenologists with sufficient experience can frequently deduce the kind of obstruction with some accuracy Most characteristic of bronchogenic carcinoma is the string like" appearance of the iodized oil on the roentgenogram

as it finds its way past the occlusion of a carcinomatous ulceration Though many non-neoplastic conditions can block or partially block bronchi, bronchographic evidence of a long, intrusive lesion strongly suggests malignancy However, a lobulated, smooth contoured obstruction is not necessarily benign In our experience, morphologically proven carcinomas have frequently been indistinguishable from typical adenomas by bronchography

In most instances, a bronchographical examination will not be undertaken until bronchoscopy has been performed since the iodized oil may considerably distort bronchoscopic appearances and make biopsy difficult Its use, then, is generally confined to situations in which the growth lies beyond the vision of the bronchoscopist It is most useful in diagnosing peripheral lesions, where the growth arises in second or third order bronchi, and is seen by ordinary roentgenology as an inflammatory process Peripheral inflammation alone almost never completely occludes the smaller bronchi, a malignant growth almost invariably does When other evidence is unavailable, many surgeons would consider such a finding adequate grounds for surgical exploration

Tomography. Tomography or laminography is a technique for rapid vibration of both x ray tube and screen, by which all details of bodily structure are eliminated except in a specific plane In general, it is used for discovering and determining the size of cavities and for exact location of various abnormalities It is of special value in the analysis of peripheral lung inflammations when there is a suggestion of malignancy, by this technique it is frequently possible to prove the presence of solid neoplastic tissue within the inflammatory shadows It may also be of value in determining how extensively lymph nodes are involved in a disease process, which may suggest a diagnosis of malignancy It may be useful also

in those instances of solid tumor obstruction of a major bronchus, outside the vision of the bronchoscopist, since it is possible to show a solid shadow within and without the bronchus in question—an appearance which is virtually diagnostic

Angiocardiography. The last radiologic technique of major significance is angiocardiography, it is as yet not very widely practiced but promises much It consists of the injection of vinyl acetate intravenously, and on over exposed roentgen film taken shortly afterwards Distortion of pulmonary vessels is a significant and readily apparent finding, more diagnostic yet is the finding of complete occlusion of several small vessels or of a pulmonary artery Since the blood vessels of the lung are highly resistent to all pathologic processes except actual invasion by malignancy, occlusion of such vessels is more pathognomonic than simple displacement Dotter, Steinberg and Holman report the diagnosis of 34 of 53 patients with bronchogenic carcinoma by the utilization of this procedure The percentage is not spectacular, but diagnosis of malignancy made by this technique is generally authorative

The fact remains, however, that roentgenology by itself is not diagnostic, and the tentativeness of suggested diagnoses arrived at by this means is much greater than a reading of literature on the subject would suggest Brower, Jones and Dolley reported several years ago 30 cases in which exploratory thoractotomy was undertaken in the expectation of finding malignancy, and in which the actual condition ranged from lung abscess and tuberculosis through the benign tumors and cysts Diagnostic techniques apparently included all the usual roentgenologic techniques, except angiocardiography Though an exploratory operation which proves the primary pathology to be pneumonitis, as an instance is a source of embarrass

ment it must be expected *from time to time and borne* with good grace We do not have an infallible diagnostic technique and it is inevitable that a diagnosis on the basis of roentgenologic findings and the clinical symptoms will from time to time prove erroneous It is necessary at times to explore patients without morphological evidence of malignancy, an exploratory thoracotomy in doubtful instances is preferable to delay

Something should be said about the small percentage of bronchogenic carcinomas found in almost every large series which were discovered by other than radiological techniques either accidentally or at autopsy after a negative x ray report had been made In many such instances re examination of the x rays in question suggests that minimal evidence of abnormality was overlooked However it must be emphasized that roentgenology cannot be regarded as proving a negative diagnosis if there is other evidence of pathology The interval of time between the inception of a microscopically identifiable lesion and a lesion apparent upon an x ray film has been variously estimated In some instances it seems to be as long as seven years Bronchography of course will sometimes give evidence of a tumor body too small to appear on an ordinary roentgenogram

Further Diagnostic Studies

5

IT MUST BE emphatically asserted that a diagnosis of bronchogenic carcinoma not based upon morphologic findings is a presumptive diagnosis actual malignant tissue or malignant cells must be demonstrated in order that a diagnosis be authoritative Where there is a presumptive diagnosis of malignancy surgery should not be unduly delayed while morphologic evidence is sought but a reasonable effort should be made to demonstrate morphologically that the abnormal process is indeed malignant When surgery is undertaken without such evidence it must be expected that a certain number of bronchogenic carcinomas will be found at exploration to be benign conditions

There are several techniques by which such morphologic evidence can be obtained (Figure 15) The identification of malignant cells in the sputum and bronchoscopic biopsy are the most important means of arriving at a morphologic diagnosis but other methods are available Excision and study of palpable cervical lymph nodes is of course a routine procedure when bronchogenic carcinoma is suspected Unfortunately if cancerous tissue is found in these nodes the lesion is already inoperable and

diagnosis loses much of its significance Potentially of much interest is the minor surgical procedure of Daniels by which lymph nodes from the deep cervical areas are excised

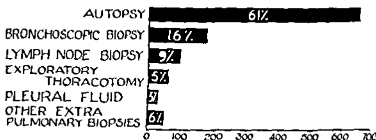


Figure 15 First method yielding histologic proof of bronchogenic carcinoma in 1 070 autopsied patients

Punch biopsy is also available for morphologic diagnosis The suspicious lesion must be carefully located by means of a correlation of posterior anterior and lateral roentgenograms or preferably the biopsy can be carried out under biplane roentgenoscopic guidance so that the exact relationship of the needle to the suspicious shadow can be determined Unless there is such guidance the biopsy specimen is likely to be withdrawn from the surrounding area of secondary inflammation rather than the mass itself This was a frequent complaint in the early experience with the technique The tissue specimen withdrawn by careful utilization of this technique is usually large enough to permit confident diagnosis

The propriety of punch biopsy is still debatable Arbuckle reports its frequent use without untoward results However the literature of a few years ago when the method was widely used contains reports of pleural implantation of malignant cells at the site of the biopsy and also occasional extension of infectious processes For this reason an exploratory thoracotomy is usually preferred when the physician is confronted with a possible

diagnosis of mnlignancy which cannot be confirmed or ruled out by the standard morphologic techniques

Bronchoscopy. It is obvious that maximum information by means of bronchoscopy requires that the primary tumor body lie near enough to the carina to be directly visualized There is a good deal of disagreement as to how many bronchogenic carcinomas fulfill this requirement (Figure 16) Although diagnosis by bronchoscopy

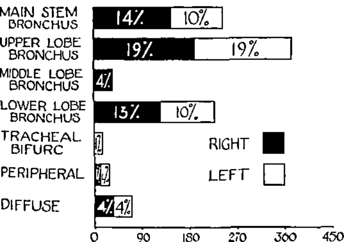


Figure 16 Location of primary tumor in 984 patients with bronchogenic Ca

has been reported in up to 75 per cent of a series most claims have been somewhat more modest Oschner reported positive bronchoscopic results in 41 5 per cent of 147 patients resected Ariel *et al* found that positive histological diagnoses depend on a good many factors beside the skill of the bronchoscopist including case selection and the willingness of the surgeon to operate without recourse to bronchoscopy Our own experience suggest that the lower figures are closer to the actual situation it would seem certain that less than half of all primary lung

malignancies lie close enough to the carina to be positively diagnosed by this technique As Figure 17 indicates much depends upon the location of the tumor a tumor of the lower lobe is twice as easy to detect as a tumor of the upper lobe

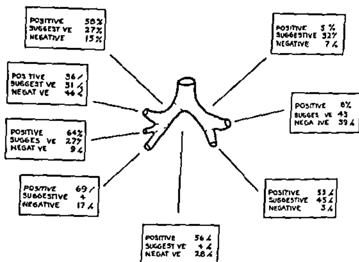


Figure 17 Results of bronchoscopy according to location of tumor in 397 patients

When it lies within the range of the bronchoscope the tumor is usually readily noticed even when quite small The normal bronchus is very regular in appearance ranging in color from a light pink to a light red and the cartilage rings are prominent and even A tumor which is macroscopically visible will usually be marked by discoloration and will be raised above the level of surrounding healthy mucosa Erosion is common Sometimes the mucosa over the growth will appear to be of a normal color but malignancy will be suggested by prominent and tortuous blood vessels over the top of the growth When there is a suggestion of abnormality which is yet unidentifiable

the presence of new growth is sometimes indicated by the irregular appearance of the cartilage as the patient breathes

The detection and evaluation of these appearances is a matter for the trained bronchoscopist but it behooves the physician to know the variations from normal which are significant

The primary service that bronchoscopy renders is to permit direct visualization of the tumor body but there are also several secondary appearances which are significant In this category is the fixation of the bronchial tree In health this system is very flexible and in constant movement While any abnormal process within the tracheobronchial tree itself or the dependent parenchyma may limit this movement particularly if such an abnormality is accompanied by pleural adhesion the limitation of movement is apt to be marked in the presence of bronchogenic carcinoma In instances fixation is almost diagnostic when the examination is made by an experienced operator

Some distortion of the bronchial tree may also be noted even when the tumor has not penetrated into the lumen Where such distortion is seen in the trachea it does not of necessity indicate actual involvement of that structure and contraindicate surgery although prognosis at this point is admittedly poor Longitudinal ridges have been observed within a bronchus which indicate external compression and strongly suggest malignancy

When bronchogenic carcinoma is suspected an important aspect of the bronchoscopic examination is a close inspection of the carina Even when the main tumor body lies entirely within the parenchyma and thus is beyond the range of the bronchoscope metastatic involvement of the subcarinal lymph nodes will frequently contribute to diagnosis At times such involvement will

be extensive and be suggested to the bronchoscopist by a pronounced widening of the carina When the metastasis is not so extensive, some lymph node involvement will frequently be indicated by the fixation of that structure Again it must be cautioned that bronchogenic carcinoma is not the only condition which produces a pronounced enlargement of mediastinal lymph nodes and the evaluation of such a finding must be made with care especially if there is coexistent tuberculosis or a history of tuberculosis

Bronchoscopy is of greatest use when it permits biopsy specimens to be taken from any abnormal areas of the bronchus Only when a positive biopsy specimen is secured is the diagnosis beyond question However when such a specimen is examined and no malignant tissue is found it does not necessarily result in a negative diagnosis It is sometimes very difficult to distinguish between a tumor body and surrounding inflammatory changes and a biopsy specimen may be of inflammatory tissue There is little serious risk in taking such biopsy specimens but small hemorrhages are sometimes occasioned for this reason the taking of biopsy specimens is usually postponed until the end of the examination

If the patient is not moribund there are practically no contraindications for bronchoscopy The only real risk in the procedure in the hands of a skilled operator occurs if there should be an area of serious ulceration or erosion in the trachea through which the bronchoscope might accidentally penetrate The procedure is however physically uncomfortable in many instances and it is an even more acute psychological disturbance in others In our experience repeated bronchoscopies often seriously enervate the patient Upon the physician then who is naturally concerned with the patient as a human being as well as a collection of symptoms with a case history

devolves the obligation of preventing unnecessary use of the instrument Where there is a presumptive diagnosis of malignancy upon the basis of symptoms and roentgenology, the surgeon should be contacted before arrangements are made for bronchoscopy, since at the present time many surgeons prefer to be present at the examination or carry out the procedure themselves

When a tumor body lies in a main bronchus or the lower or middle lobe bronchi, there is a good chance for immediate and positive diagnosis There seems little likelihood however, that the effectiveness of bronchoscopy will be greatly extended beyond what it has at present A mirror arrangement has been developed which, to a limited degree, extends the range of vision and increases the possibility of upper lobe lesions being visualized There are also available specially designed forceps by which biopsy specimens can be taken beyond the range of bronchoscopic vision In some instances better visualization of an upper lobe bronchus can be obtained by establishing a pneumothorax prior to the bronchoscopic examination Each of these developments has proven, upon occasion, to be of real service, but they have not materially overcome the expected limitations of bronchoscopy It is difficult to foresee any possibility that such refinements of technique will be statistically significant, it would seem that in any large series of unselected cases, morphologic diagnosis by means of bronchoscopy cannot be expected to exceed 60 per cent

CYTOLOGIC DIAGNOSIS

Like bronchoscopy, cytologic diagnosis is something short of the infallible diagnostic approach that is desirable However, present evidence indicates that if the technique is properly applied, the percentage of positive diagnosis that can be made is substantially higher than the per

centage of diagnoses made bronchoscopically How effective cytologic diagnosis will eventually prove to be is still doubtful, the application of cell studies to lung secretions is still so new that it is difficult to predict its potentialities

Of one thing, however, we are quite convinced In proper hands, a cytologic diagnosis, "consistent with malignancy," is morphologic and it is as reliable as a diagnosis based upon biopsy material This has been the first concern of the students of cytology In our laboratory at the San Francisco Hospital, we have found that our accuracy in avoiding false positive diagnoses approaches 100 per cent in a total group of over 2,500 patients suspected of lung cancer

The technique has a major advantage over other means for morphologic diagnosis in its simplicity for the patients The sputum submitted for examination must be raised from the bronchial tree, secretions from the throat and upper part of the respiratory system are uninformative It has been alleged that a fairly large proportion of patients will not raise such sputum, but in our experience if the raising of sputum is insisted upon with sufficient firmness, an amount sufficient for cytologic examination can almost always be collected The sputum which is commonly raised in the morning, just after the patient wakes, is generally the most satisfactory There is the additional requirement that such a sputum sample be processed before the cells have time to degenerate The interval that can lapse between raising the sputum and its processing varies with its moisture content, but ordinarily it should be smeared within three hours of being raised As long as the sample is not allowed to dry, however, cells may retain their distinctiveness for a period of 10 hours The procedure is, then, of utmost convenience Sputum samples can be collected repeatedly without the slightest interference with other diagnostic techniques

Little special training is necessary for the procedures preliminary to staining Slides must be previously prepared by being thoroughly cleaned and marked with a diamond pencil, and cover slips must be available Ordinarily the accuracy of the diagnosis is increased by selection of the material to be smeared We have discovered that malignant cells are most apt to be found in opaque, granular bits of tissue, white to yellow in color Some experience is necessary to distinguish these particles from bits of food or pus Where such tissue flecks are not observed, blood flecks should be chosen This selection of materials to be smeared is best accomplished by pouring the sputum sample into a watch glass and examining it against a black background

Specimens selected for smearing should be removed from the sputum sample with rat toothed forceps, cut loose with scissors if necessary, and deposited on the previously prepared slides They should be smeared upon the slide as gently as possible We have found the best procedure to be the teasing of the specimen across the slide with a wooden applicator Immediately upon smearing, the slide should be deposited in a fixative It is most important that the slide not be allowed to dry Even a moment's delay between smearing and fixation may result in some drying at the edges of the slide, resulting in loss of cellular outline and changes in the staining reaction

Ordinarily three specimens should be chosen and fixed from each collection of sputum By this practice it is possible to cover the entire range of macroscopically suspicious material present Paper clips on alternate slides will prevent contact of the smeared surfaces in the fixative

The fixative solution consists of equal parts of ether and 95 per cent alcohol When specimens are being prepared for mailing before they are to be stained, they

should be left in this solution two hours (If staining is to follow immediately, a half an hour is sufficient) After two hours in this solution the slide can be removed, air dried and packed for shipping the smeared surface protected from dust After a slide has been prepared it can be permitted to stand for seven days if necessary without loss of cell detail Throughout the handling of the slide, especial care must be taken to prevent the contact of slides one with another, since cellular elements can be thus transferred

Ordinarily, the referring physician's responsibility ends at this point, the slides are stained and examined at a laboratory However, the staining and preliminary screening can sometimes profitably be done by a specially trained laboratory assistant who can eliminate from consideration those slides which show no abnormal cells Final diagnosis, however, must be made by a pathologist who has been further schooled in this technique One of the disadvantages of cytologic diagnosis is that its effectiveness requires the services of a pathologist with extensive experience with cytological appearances

The reason that experience with cytologic diagnosis is necessary for accurate evaluation of cytologic findings is that the criteria for malignancy by this technique are different from those of tissue sections A pathologist is accustomed to depend to a considerable degree upon histologic structure and evidence of invasiveness These malignant characteristics are not seen in cytologic specimens The cytologist must make a diagnosis on the basis of relatively few cells which are isolated As a consequence it has been necessary to discover criteria for malignancy which depend upon the appearances of cells rather than upon determinable cell behavior

Furthermore there is no single criterion of malignancy a diagnosis must be made upon the conjunction of

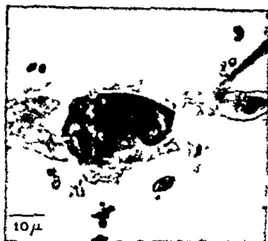
several cell abnormalities These can be roughly divided into seven groups (1) Cell size (2) Nuclear predominance (3) Irregular nuclear contour (4) Hyperchromatism (5) Nucleolar increase (6) Mitoses and (7) Cell groups (Figure 18)

Cell size is significant to diagnosis both absolutely and relatively It has long been recognized that cell hypertrophy is a frequent manifestation of malignancy We have found that cell enlargement is critical to diagnosis as it approaches an actual doubling of normal cell dimensions We have never seen a benign cell in which there is a two fold enlargement of nucleus and cytoplasm over normal though such an enlargement is common in the presence of malignancy Enlargement of the cytoplasm alone is not diagnostic enlargement of the nucleus alone (to greater than 20 micra in diameter) is presumptive but not diagnostic

A variation in size from one cell to another may also be of importance but to evaluate the significance of such variation requires a good deal of experience a certain amount of such variation is of course to be expected among normal cells

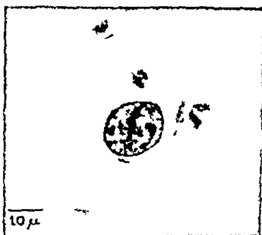
Nuclear irregularity Here again experience is necessary for an evaluation Normal cells have frequently some distortion of nuclei However distortion of normal cells is usually seen to be due in torsion or buckling a nuclear distortion significant to diagnosis seems independent of exterior force Such distortion is usually seen as sharp extrusions or lobulations

Hyperchromatism This is the classic abnormality of cancer cells and under certain circumstances it may be regarded as diagnostic without further evidence of abnormality Massive irregularly distributed chromatin condensations are the most unmistakable evidence of hyperchromatism but chromatin knots and thick nuclear rims



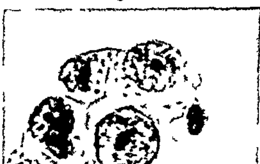
1





3







may also be important indications of malignancy Care must be taken, however, to distinguish these latter features from the appearances resulting from over-staining

Mitoses. In cytologic examination, unlike tissue sectioning, this criterion is not of much importance Mitoses are seen occasionally, but by themselves they are never diagnostic

Nucleolar aberrations Nucleolar aberrations are very common indications of malignancy Rarely a single nucleolus will be seen which is so large that by itself it is almost diagnostic of malignancy More commonly, a significant aberration will take the form of multiple, moderately enlarged nucleoli Such appearances are important

Figure 18

← Plate 1 (Sputum) Multilobulated malignant nucleus showing massive chromatin condensations The contrasting clear areas afford reassurance that there has not been a technical overstaining with hematoxylin Note also the normal staining of the nearby polymorphonuclear leucocytic nuclei The cytoplasm is abundant and shows considerable vacuolization or reticulation This appearance is quite common among malignant cells but is also seen in histiocytes

Plate 2 (Sputum) The heart shaped malignant nucleus shows an abnormal clearing which contrasts with the thick nuclear rims and with the coarse chromatin condensations The two oval nuclei above and to the left are truly hyperchromatic but because of the diffuseness of the staining they can only be judged by the overall staining of cells on the slide

Plate 3 Malignant cell with nuclear predominance The nuclear diameter is roughly 18 micra No other cytological aberration is present Cells of this size with the degree of nuclear predominance have never been seen except in association with carcinoma

Plate 4 Lobulated (multinucleated?) malignant cell Note the inequality of the lobes The course irregular unequal chromatin granules are diagnostic

Plate 5 Malignant squamous cells showing marked hypertrophy Intercellular bridges are faintly seen on this picture There is no evidence of cornification In addition to the marked general hypertrophy other signs of malignancy are the prominence and sharp angulations of the nuclear rim and the prominent nucleoli

Plate 6 Malignant cell group showing variation in size Even without the huge cell the others of the group show sufficient variation in size to be suspicious Note the vacuolization in many of the cells in spite of the fact that they arose from a squamous cell carcinoma

but it must be remembered that these structures may vary quite widely in non malignant cells

Cell grouping The significance of this arises from the tendency of malignant growths to fragment to disintegrate into cell clumps which seem to be a unit of growth When such clumps are found in the sputum they are easily distinguished from normal exfoliated epithelium by their smooth configuration as compared with the rough jagged appearance of epithelial sheets and by a crowded appearance characterized by prominent nuclei and a mutual nucleolar distortion

It is apparent that cytologic diagnosis cannot be a mechanical process Because very few single appearances are in themselves pathognomonic a confident diagnosis of malignancy depends upon an evaluation of microscopic findings Since the distinction between benign and malignant is very often a distinction between degree of aberration a positive diagnosis requires that more than one criteria for malignancy be fulfilled

At first sight this might seem a dubious diagnostic procedure But it must be remembered that a diagnosis of malignancy on the basis of a tissue section also requires evaluation although perhaps to a lesser degree *A cytologic diagnosis is not less reliable than a diagnosis* based upon a biopsy specimen its criteria are different not less reliable

At the same time cytologic studies have distinct advantages over other methods of diagnosis Most important is the fact that the wet smear when properly handled preserves cell size and shape far better than is possible by other methods of fixing tissue for pathologic study Tissue dropped into fixative shrinks markedly under the best circumstances In the process of wet smearing on the other hand the cells are flattened onto the slide and adhere to it so that marked shrinkage cannot occur The

appearance of the cells as seen by the cytologic method is then nearer the appearance that the same cells would have if it were possible to examine them *in situ* without staining As a consequence criteria for malignancy such as cell size, nucleocytoplasmic ratio and nuclear contour can be depended upon Because the nature of malignant cells can be accurately visualized by this technique it is hoped that cytologic studies will eventually contribute to our understanding of the process of malignant change

A disadvantage of cytologic diagnosis is that it is impossible to eliminate the element of chance Every tissue malignancy is presumably disintegrative in its essential nature and constantly throws off live cells from the tumor body into adjacent cavities and tissues Since according to most present day investigators bronchogenic carcinoma originates in the basal layer of cells in the bronchi it is obvious that in a majority of instances some cancer cells will penetrate into the bronchial secretions and be available for cytologic identification Theoretically then almost all bronchogenic carcinomas should be diagnosable by this means There are however clinical limitations In the first place if diagnosis is not made before the tumor occludes the bronchus of origin adjacent inflammation may completely seal off the body of the tumor from access to the trachea and in this case malignant cells cannot get into the sputum The second major difficulty is that the penetration of such cells into sputum is apt to be intermittent Although cells are exfoliated by malignant growths in the lungs in countless numbers not every collection of sputum will contain such cells In our experience malignant cells are frequently demonstrated intermittently in patients with known malignancies

Because of the intermittent appearance of malignant cells in sputum maximum use of cytology depends upon an adequate number of sputum samples being examined

In a recently reported series of cases, we were able to make a positive diagnosis by cytology in 125 cases of 241 bronchogenic carcinomas proven by other pathologic methods This is an accuracy of only 52 per cent However, in 32 of the 116 missed cases only one sputum sample was examined, and in a majority of these 116, less than five separate collections were examined We have found that when five sputum collections are made for each patient, an accuracy of about 90 per cent can be anticipated Cytology is, then at least potentially more useful to diagnosis than bronchoscopy

We have repeatedly attempted to improve the diagnostic accuracy of cytology beyond 90 per cent by persistent examinations However, we have found that if malignant cells do not appear in the first five specimens, *they are very unlikely to appear subsequently In most* instances this failure seems to be due to the fact that the tumor does not adjoin a patent bronchus, but we have been unable to prove that this invariably is the case

It cannot be assumed then, that cytology will replace bronchoscopy, but it becomes increasingly apparent that it will do much to repair the deficiencies of the older method As an example, 70 of the 241 previously mentioned patients with bronchogenic carcinoma had peripheral lesions Such lesions are more apt to be amenable to surgery than lesions close to the hilum We were able to diagnose 36 of these lesions positively by cytology, whereas by bronchoscopy only ten of them were singled out as suspicious for malignancy" on the basis of secondary findings If five specimens had been available for each patient cytologic diagnosis would have been possible in many more instances

There is also some evidence that cytologic diagnosis is particularly effective when the malignant lesion is in its earliest stages of development The free movement of

secretions is an important factor in this situation, but in our clinical experience with the technique we have frequently had the impression that younger and smaller lesions oftentimes throw off more cells into the secretions than older ones The diagnostic value of this observation is obvious

A modification of the cytologic technique, bronchology, is also of some promise In this procedure, bronchial secretions are gathered before a biopsy is taken at bronchoscopy Where secretions are not present in sufficient quantity for suction withdrawal bronchial walls can be swabbed, or suspicious bronchi flushed with saline solution The secretions are then prepared in exactly the same way as sputum for cytological examination Herbut reports that this procedure had added 20 per cent to his diagnostic efficiency Such an examination should be undertaken whenever a bronchoscopy is done

As has been said, the technique of cytologic diagnosis has not been thoroughly evaluated It is without question a major advance in the diagnostic armamentarium of the physician, but the proper application of the method for maximum effectiveness has not been determined The first problem has been to establish its reliability this has been accomplished to a considerable degree For some time Woolner and MacDonald have been advising exploratory operations on the basis of cytological findings In 40 per cent of the 70 patients reported upon in their recent study surgical exploration was undertaken upon the basis of cytologic findings, without other morphologic evidence of malignancy We believe this to be a rational procedure

The greatest value of cytology might seem to be in periodic examinations for males over 40 Although the examination of slides is time consuming, and therefore somewhat expensive, the fact that cytologic diagnosis can often give certain evidence of bronchogenic carcinoma

before the tumor body produces definite roentgenologic changes suggests that maximum utilization of the technique would include routine smears In any case it can be the most valuable single diagnostic device for the investigation of minimal symptoms where malignancy is even a remote possibility The more extensive use of cytology which can be expected in the near future will without doubt markedly increase the percentage of bronchogenic carcinomas which are amenable to surgery

Surgery | 6

ONE OF THE most impressive achievements in the history of medicine is the virtual perfection, in the short space of 18 years, of the technique of pneumonectomy. Since the pioneer work of Graham and Reinhoff, almost every specialist in the field has contributed to the development of the operation. As compared to an expected operative mortality of around 50 per cent in the years following the introduction of total pneumonectomy, a patient today has between 90 and 95 per cent chance of surviving this radical procedure. Even these figures slight the magnitude of the achievement, because today surgeons are able to operate on almost everyone who might be benefited; the 8.4 per cent operative mortality that Graham reported recently was sustained in a group of patients in which the elaborate criteria of operability of former days was not necessary.

Although lung surgery is being increasingly applied to the treatment of other chronic pulmonary conditions, it is preeminently the treatment for bronchogenic carcinoma. At the present time, it is the only method that offers any hope of cure, and it is perhaps even the only method which favorably effects the course of the disease. It is the technique toward which the physician who diagnoses bronchogenic carcinoma hopes to direct his patient.

However, as has been sufficiently emphasized already in the course of this monograph, a great many patients

with bronchogenic carcinoma are already obviously inoperable by the time the condition is diagnosed Statistical reports on the exact percentage of patients unsuitable for surgery show a considerable variation, and it is difficult to arrive at a representative figure In surgical clinics there is apt to be a fairly high percentage of operable cases simply because many of the inoperable ones have been recognized in early diagnoses and have not been referred for surgery The attitude of the surgeon is also apt to influence this proportion Graham reports about 40 per cent of his patients at present are worth operating upon, this probably represents the highest possible estimate for the overall, inclusive situation (which must include city and county hospitals where the disease is more apt to be far advanced when discovered)

In a great percentage of the patients who reach the operating table, an exploratory thoracotomy reveals the growth to be inoperable and a pneumonectomy is not performed Graham, who is conservative in selecting patients for surgery, is able to proceed to pneumonectomy about 65 per cent of the time Surgeons who perform thoracotomies more readily are apt to be able to continue to pneumonectomy less often Rosemond performs pneumonectomies at present upon about 55 per cent of all who are thoracotomized Lindskog and Bloomer, who did about the same percentage of pneumonectomies between 1945 and 1948, as compared to an earlier figure of 38 per cent, felt the improvement was due to an increased number of pneumonectomies for palliation Hence, 50 per cent can be taken as a representative mean So far as the technique of the operation is concerned, it is hard to see how this figure can be improved upon, a pneumonectomy for bronchogenic carcinoma at the present time frequently includes resection of invaded areas of the visceral pleura, the chest wall, the diaphragm and even cardiac tissue

The real question concerns the percentage of patients who are enabled to live a substantially longer time because of the surgical removal of a carcinoma The determining consideration is not entirely the question of the five year cure possibility but of the material increase in life expectancy that can be anticipated This figure is extremely hard to estimate it is complicated by the fact that the willingness to undertake ever more radical excision of invaded contiguous areas will presumably increase this percentage somewhat over our previous experience It is our impression however that in at least 40 per cent of the patients receiving a pneumonectomy there is no evidence of a material increase in length of life

We have carefully reviewed 241 cases of bronchogenic carcinoma from various sources * these illustrate what we believe to be a representative situation so far as the operability of lung malignancy is concerned These patients were found to have the disease at these institutions between April 1947 and May 1950

		Survival Time Average	*Percentage of Total*
Group I Clinically inoperable—117 patients			48 5%
Expired	114 Cases	11 4 Weeks	
Alive	3 Cases	91 2	
Average		13 4	

* Source of material

University of California Hospital	83
San Francisco City and County Hospital	60
Stanford University Hospitals	6
County Hospitals and Tuberculosis Sanitoria	23
Government Hospitals	23
Private Hospitals and Physicians	26
Total	241

Group II	Explored but not resectable—50 patients			20 8%
	Expired	49 Cases	24 0 Weeks	
	Alive	1 Case	61 0	
	Average		25 0 "	
Group III	Explored and resected—74 patients			30 7%
	Expired	64 Cases	37 7 Weeks	
	Alive	10 Cases	96 0 "	
	Average		44 4 "	

As can be seen only 10 patients of the 74 resected are still alive at an average of about one and one half years after the pneumonectomy This is a salvage rate of roughly 4 per cent of the whole group of 241 patients—hardly an encouraging finding The five year cure rate will undoubtedly not exceed half this percentage

The major effort of all members of the medical profession is naturally directed to increasing the percentage of cures"—interest centers around the 10 per cent or so whose life expectancy can be substantially increased by surgery

The whole cancer program is properly devoted to obtaining a further increase in the size of this group The limitation of surgery however is readily apparent Given the same overall proportion of patients who prove beyond the help of pneumonectomy at thoracotomy and with the same rate of recurrence and the possibility of materially improving either figure to any great extent is a remote one Even if the speed and accuracy of diagnosis can be doubled at least four out of every five patients who have bronchogenic carcinoma will still remain beyond the help of the surgeon

It is proper that the main effort of medicine should be directed toward an increase in the number of surgical

cures no matter how difficult this may be However the individual physician cannot limit his concern to the two in 20 or even the hoped for four in 20 patients who are within the reach of surgery These patients who are doomed and who are in the majority are not the less entitled to the maximum effort of the doctor Surgeons often speak of their radical techniques as salvaging it is a useful concept By a program directed to the total care of the patient including his psyche there is some thing to be salvaged even in those patients who are in eligible for pneumonectomy at diagnosis

Something will be said later of the means available for the management of those patients who are deemed to be inoperable at diagnosis the point here is that well over one fourth of all patients with bronchogenic carci noma are not in our calculations receiving the attention to which they are entitled The whole group of patients who are subjected to operative procedures which do not materially increase their life span are to some degree actually mishandled So long as surgery is our only ap proach to lung cancer the ideal is two groups of patients —those who are inoperable at diagnosis and those who are resected and cured Needless to say this is a theoretical ideal it could only be attained by a procedure which would radically reduce the percentage of cures which are now achieved The effort however must be directed to ward a substantial reduction of the group of patients who are now subjected to surgery without material benefit

Again this responsibility is one which inevitably must devolve upon the physician making the diagnosis The responsibility cannot be evaded by referring to surgery all patients in whom carcinoma is found the diagnosis must include an opinion as to operability If there is a chance of cure surgery should be requested without hesi tation or delay but the physician must be as certain as

modern techniques permit that there is indeed a chance of cure The terrible psychological consequences to a patient when he has been prepared for a pneumonectomy for the cure of bronchogenic carcinoma, and then must be told that the operation is not feasible, are memorable very frequently the doctor, as a human being, must regret that the patient came off the table alive The situation is hardly better in the case of recurrence On the other hand, if the patient is recognized as inoperable when the condition is diagnosed, a physician making full use of the modern armamentarium of drugs, and with the co operation of relatives—and perhaps with a special capacity for reassurance—can help the patient make good use of the time which remains

The object, then, should be toward full diagnosis before surgery referral, and such a diagnosis involves a maximum effort to evaluate operability. The basis of such an evaluation is a further physical examination after the diagnosis of bronchogenic carcinoma, morphologically proven or presumptive, has been made It needs to be the classic painstaking, tedious and thorough examination supplemented by extensive roentgenologic examinations as suggested by the physical examination, and any other technique that promises information

Of course, the findings of the bronchoscopist are critical, an invaded trachea, a tumor too near the carina to permit surgical closure, a rigidly fixed trachea, are all immediate contraindications Even moderate hoarseness, implying involvement of the laryngeal nerve and some paralysis of the larynx, or a paralyzed diaphragm, may likewise be contraindicatory If such signs are lacking further investigation into the relation of the tumor to the mediastinum should be made roentgenologically Correlation of posterior-anterior and lateral films will some-

times determine whether or not there is mediastinal in volvement When the tumor is thought on the basis of such a correlation to lie suspiciously near the central shadow, edema of the face and neck even though mini mal will confirm vena caval involvement

An angiocardiographic examination may be very help ful in this presurgical study Dotter Steinberg and Hol man in a recent study of the subject suggest four posi tive angiocardiographic findings which are considered evidence of inoperability in the presence of bronchogenic carcinoma They are

1 Partial or complete occlusion by tumor of the left pulmonary artery within 1 5 cm of its site of origin or of the right pulmonary artery proximal to its point of bifurcation
2 Partial or complete occlusion of the great mediastinal veins due to tumor or polypoid defects within the superior vena cava
3 Mediastinal metastases seen by contrast delineation of displacement and deformity of adjacent vascular structures indicating external pressure
4 Localized thickening of the pericardium in the ab sence of pleural disease and adjacent tumor

Though angiocardiography has not been completely evaluated its promise to preoperative examination is en couraging

There are in addition other specific signs of medias tinal abnormality which when a bronchogenic carcinoma has been demonstrated will normally be referred to that condition and which will indicate inoperability Any [illegible]

gree of extension into the anterior mediastinum Perhaps

the most important technique, however, is the careful elicitation of even minor symptoms as *guides to further investigation*

Such attention to symptoms is even more important as a guide in the search for metastases The fact that cancer cells which reach the blood stream from the lung pass directly through the heart into the great vessels make metastatic manifestations protean Analyses of such metastases on the basis of collections of case histories, such as the one listed before, are more of an indication of the range of possibilities than an actual guide Next to the history and symptomatology, the most important procedure is a careful palpation of the patient's body, with particular attention to the liver, spleen and lymph nodes In our series, we found that metastases to the bone was accompanied in every case by pain so the skeletal system need not be of particular concern unless there are symptoms referable to it The whole procedure otherwise should be conducted with a maximum of suspicion, and the patient should be immediately referred to an appropriate specialist when an abnormality is found that might even remotely be related to the bronchogenic carcinoma It should be noted that when the patient knows that cancer is under consideration, the resulting psychic disturbance is apt to be difficult to distinguish from the symptoms of a central nervous system lesion, a psychiatrist can often help determine whether or not there is an organic basis for the psychic disorder

Again it should be emphasized that the object of this examination is to spare the patient the discomfort, mental distress and expense of an operation which cannot materially benefit him As such, it is necessary that inoperability be proven by morphologic methods or the strongest of presumptive evidence When such evidence is not forthcoming, exploration must be undertaken

If the patient is not proven to be inoperable after a thorough examination, he should be referred to a chest surgeon without delay The responsibility of the physician is here more or less at an end We have found that it is of help to the patient, and frequently also to the surgeon, if the patient is told in a general way what he may expect while under the surgeon's care The latter cannot be expected to have the time to establish the personal relationship with the patient that is so important a part of the physician's services, and something can be contributed to the operative procedure if the physician will take time for reassurance and an explanation of the preoperative procedures that the surgeon is apt to require The general supportive intention of venoclysis, when it seems likely to be called upon, should be made clear, and the importance of injections and aerosol antibiotics toward minimizing postoperative infection should be explained The function of the preoperative pneumothorax may be discussed, and the patient should be prepared for further bronchoscopy if the surgeon so requires In general, the patient should be warned that his stay in the hospital prior to the operation will be occupied with numerous but routine measures When he is not so prepared, the patient, who is already disturbed by the seriousness of his condition, is apt to regard these measures as a series of alarming emergency procedures He should further be informed that for a short time after the operation there will be some difficulty with tracheal congestion and that for a few days drainage of the thoracic cavity is routine procedure

The subsidiary techniques of continuous administration of whole blood to maintain normal blood volume, and control of lung function by intratracheal intubation, are very important to the relatively low hospital death rate that is found in these cases at present The administration

of a general anesthesia by a closed system with the intra bronchial tube is perhaps still the general practice, but Overholt prefers paravertebral block and local infiltration with general anesthesia available for use whenever its analgesic effect is desirable

The operative approach is made anteriorly (Reinhoff) or posterolaterally (Overholt) The latter generally involves resection of the sixth rib When the diagnosis is in doubt, a frozen section of the abnormal tissue can be made and examined without delay as soon as the chest wall is open, where such tissue is not readily found a pathologic examination of mediastinal nodes will prove or disprove bronchogenic carcinoma with some degree of accuracy At this point the surgeon can also estimate operability in terms of extension Closure of the bronchial stump, which in the past has been a weak point in the pneumonectomy procedure, is now accomplished by ligature 1 cm or so above the bronchial stump, fibrinous clotting in the proximal end helps secure an airtight closure, which is then covered by a pedicle flap of parietal pleura In this way closure does not indefinitely depend upon the suture, which tends to cut through the bronchus

Although pneumonectomy is a highly developed art today, about one out of five patients die within a month of the operation The chief cause is postoperative cardio vascular failure If the patient survives the first month, it is unlikely that he will die directly from the operation thereafter, but recurrences within the first year are very common Total pneumonectomy is not without its physiological sequelae, ordinary occupations and light activity can be pursued in most cases, although there will be a tendency toward dyspnea After five years or so, the overdistended lung that remains is apt to lose efficiency Overholt and Schmidt report two of ten five year cures to be respiratory invalids For this reason some surgeons

prefer to follow a pneumonectomy with thoracoplasty, since the remaining lung is more efficient if its distension is limited There is a conviction in some observers that a patient who has had a pneumonectomy is especially subject to right-sided heart failure

It has been generally assumed that the only rational approach to bronchogenic carcinoma was one which included the widest possible excision of possibly invaded tissue on the analogy of the radical mastectomies done for breast cancer The subject has been to some extent reopened by the report of Churchill and his associates, on the favorable results obtained in selected cases with a lobectomy Although they refrain from drawing conclusions, their experience with the less radical technique suggests that if the tumor has not extended beyond the limits of a lobe, and perhaps if the mediastinal nodes are not grossly involved, a lobectomy may be as efficient a technique as a pneumonectomy Which operation is to be undertaken is, of course, a matter for the decision of the surgeon at the time of operation, but it is interesting to note that lobectomies are not absolutely contraindicated in instances of bronchogenic carcinoma The advantages of the less radical procedure to the patient postoperatively are substantial

Nothing has been said so far about the so called "palliative pneumonectomy" This procedure is the subject of a great deal of disagreement, and probably in such instances all extreme statements are exaggerations As operative mortality has been reduced, there has been a tendency to operate on every lung cancer patient who is not immediately seen to be beyond help, this procedure is frequently justified by the assertion that palliation is at least possible In our opinion, this point of view is to be deplored The palliation achieved by radical excision cannot be used as a means of evading diagnostic responsi-

bility The patient should not be encouraged to submit to radical surgery until there has been a realistic appraisal of its possible benefit On the other hand, when a patient has been explored in entire good faith and found to be inoperable, and there are large amounts of infection in the carcinomatous lung, palliation by pneumonectomy *is justified It is true, likewise, that a low grade squamous* carcinoma can kill a patient by rotting away portions of the lung, in spite of the physician's best efforts, in these instances, a pneumonectomy can be undertaken even when there is no hope for cure It is our impression that the average patient with an inoperable bronchogenic carcinoma is better off, all things, including his mental attitude, considered, if palliation is less radical Except when the lung is rotting away, a flexible use of massive doses of antibiotics will usually be adequate to control the infection in the relatively short time the patient has left Even though the infection remains troublesome, we believe this symptomatic treatment is superior to a radical and hopeless procedure involving shock, hospitalization, and most of all, excessive psychologic disturbance for the patient

Care of the inoperable cancer patient. Close rapport between patient and physician is always desirable, in the presence of a malignancy *it is a vital necessity At every* point in the diagnosis and treatment of the patient with lung cancer, his confidence in the physician is absolutely indispensable, it is a *sine qua non* The operative mortality and postoperative death rate attendant upon thoracic procedures is still appreciable, for this reason an exploratory operation without morphologic proof of malignancy absolutely demands that the patient be given a careful and realistic presentation of the "hard facts" He will accept such "hard facts only if his trust in the diagnosing physician is complete If an operation is undertaken and is successful, only the physician can relieve the patient of

his fear of recurrence As to the inoperable patient or the patient with recurrence his mental stability is very apt to depend upon the faith he has in his doctor Every physician will have his own approach to this problem of gaining the patient s confidence It must be emphasized however that the effort to win the patient s trust must be begun early and exerted continuously It is not easy to make a diagnosis of malignancy and then try to win the patient s confidence

It is generally desirable to introduce the idea of cancer early in the diagnostic procedure of any male patient over 40 We have found it useful to tell every such patient that he is suspected of serious disease such as tuberculosis cancer or syphilis and that the physician is obligated to suspect and eliminate the worst We have found that by introducing the subject of malignancy into the conversation during the patient s first or second visit he is enabled to accept the possibility and defend himself against its implications by making light of it Also the very fact that cancer has been introduced into the conversation casually very often permits him to unburden himself of his fear on the subject such an unburdening establishes immediately rapport between patient and physician that might otherwise require weeks to develop We have not found cancerphobia to result when the subject is introduced in an off hand manner and the gain to the patient and physician if a diagnosis of malignancy must later be made is considerable

The real challenge to the physician s art is the patient who is inoperable at diagnosis or who has postoperative recurrence It is seldom advisable to attempt to conceal such a finding such an attempt usually results only in a loss of confidence in the physician On the other hand it is not necessary to elaborate on the diagnosis If after the initial disclosure the patient is allowed to take the lead

in the conversation he will usually indicate the attitude toward the diagnosis that he would like to take If the physician will follow such a lead the patient is enabled to accept the diagnosis with a minimum of psychic shock and the sense of comradeship thus established between patient and physician in entire agreement can be very *helpful*

It is most important that the patient feel that every *thing possible is being done In many instances he will* put off the consequences of the disease by depending upon the discovery of a *miracle drug* This attitude will do him no harm He should be examined frequently and every new symptom should be evaluated and if necessary countered with a new drug or a new combination of drugs Repeated laboratory examinations can be made as suggested by symptoms From the physician s point of view these procedures may seem a waste of time For the patient however they will be concrete evidence that everything possible is being done By deeply concerning himself with minor developments the physician can re lieve the patient of some of the anxiety attendant upon an *incurable condition A patient with inoperable broncho* genic carcinoma should be kept ambulatory to the last *possible moment Many of them are happiest if they can* continue to be of service to their family and they should be permitted to pursue their normal occupations if they care to Many can become engrossed in an accentuation of their normal social patterns in shopping and attending the theater Others can fulfill themselves in a certain sense by doing those things to which they have always looked forward In any case every effort must be made to keep the patient occupied and interested in things about him

A major service that the physician can perform is to lend the *weight of his* counsel to the patient s own im

pulses The patient may be happiest if he remains at home but too frequently his family will be merely a reminder of what he is losing in such cases he may prefer to take up his residence at a hotel Not infrequently he will actually want to remain at the hospital where he has been sent for observation and where because of his condition he has become an important person

There is no doubt that by a careful control of pain and infection and a proper use of diet and dietary supplements a patient s life can be materially prolonged beyond that to be expected if he were not intensively treated One is never more impressed with the possibilities of morphine and the entire field of narcotics than when they are utilized in various disguises in the treatment of bronchogenic carcinoma Scopalamine can be added to standard narcotics as in Scheslinger s solution to give the patient a mental lift without his being aware of the reason Use of the various synthetic preparations which stimulate such as dextro amphetamine sulfate (Dexedrine S K F) can alleviate depression and anxiety In general it is best to prevent difficulty rather than alleviate it drugs can be used liberally

At times the patient s family can be more difficult to manage than the patient himself Their contradictory reactions and desires can completely exhaust the ingenuity and the nervous system of the physician At least one responsible member must know the complete facts usually the patient will indicate the member of the family who should be informed However it is often best if those outside the immediate family are not told Where the family group is large their frequent inquiries and advice can be extremely trying but if the physician has accepted the care of the patient he must do his best in this difficult position He cannot afford to minimize the importance of the family and the value of their help

As difficult and exhausting as the care of an inoperable patient may be, there is truly no greater challenge to the physician in the exercise of the art as well as science of medicine There are very few instances in which he can be so confident of the value of his services

This, then, is the general relation of surgery to the overall care of the patient with bronchogenic carcinoma at the present time As has been said before, major improvement in this dim picture can come about only by earlier diagnosis, and it would seem that the effectiveness of surgical techniques, even with greatly improved diagnosis is still limited to a serious extent by the nature of the disease At best, the physician is confronted by a difficult problem in evaluation He must make maximum use of the only technique which offers any possibility of cure, but at the same time, he cannot evade his responsibility to the patient by cultivating an overly optimistic view of the possibilities inherent in surgery His appraisal must be realistic, and his decisions are critical in many *respects, since he is the only one in medicine* who can be expected to give due weight to that inestimable factor, the personality of the patient

Nonsurgical Techniques | 7

Any discussion of chemotherapy as a method of treating bronchogenic carcinoma must have something of the character of a prophecy There has been nothing brought forward which has even approached in its effect upon any malignancy the criteria of a cure However substances have been developed which are carcinoid which have proven themselves to have an adverse effect upon malignant tissue even when that tissue is bronchogenic carcinoma We have drugs at the present time that kill cancer cells although they are not effective enough to kill all cancer cells in any patient They demonstrate nevertheless the possibility of a successful chemotherapeutic agent for malignancy being developed and they suggest the general areas of drug therapy in which a cancer cure is most likely to be found The subject is particularly worth the attention of students of bronchogenic carcinoma because it is impossible that a quarter of lung cancer patients can be cured by other means

Hormonal therapy Tumor therapy by means of drugs can take one of two directions In the first place a tumor can be approached by an attempt to alter radically the environment in which it arose and to which it is accustomed This is hormonal therapy In the treatment of certain malignant growths this approach has been of

substantial service Estrogens have been used to induce prolonged remissions in breast cancer in postmenopausal women and these substances have also had a marked palliative effect in cases of inoperable prostatic cancers Testosterone on the other hand has been effective on occasion in the treatment of breast cancers in premenopausal women Lastly progesterone has at times induced local regression in inoperable carcinoma of the uterine cervix

As these examples indicate hormonal therapy is chiefly of use in the treatment of malignancies of sex conditioned tissue This may well represent our rudimentary knowledge of hormones and their operation however and not be an essential distinction between sex tissue malignancies and malignancies of other systems or organs Lung tumors may prove to be as dependent upon hormonal factors although less obviously as prostate tumors

The real question in regard to hormonal therapy concerns the autonomy of malignant growths In the experience that has been accumulated in the use of hormones for the treatment of malignancy it has become evident that we must modify our concept of cancer Malignant growths are *not necessarily autonomous* Particularly in experience with prostatic cancers it has become obvious that a tumor may be fulminating and still be dependent upon certain hormones of the host Often it is years before these growths become truly autonomous

There is a great deal of clinical evidence to suggest that bronchogenic carcinoma also depends for its genesis or its progress upon a particular hormonal substrata in the host A delay of up to nine years has been noted between exposure to a carcinogen and the inception of a clinically detectable cancer a fact which clearly implies the necessary operation of hormonal factors In the past we have had no way to investigate the status of such pa

tients in the interval between exposure and the development of a macroscopically visible tumor body scattered reports of findings discovered at autopsy in accidental deaths suggest that small clusters of tumor cells may remain *in situ* for an indefinite period before a frank lesion develops If the routine use of cytology confirms this supposition it may be that we shall be able to delay or prevent the development of autonomous tumor bodies by hormonal treatment It is possible that hormones will become a major weapon in the control of lung malignancy in coming years

Specific chemotherapeutic agents At the present time however the avenues of direct attack upon the tumor cells themselves seem to have more immediate promise Chemotherapeutic agents aim at a direct effect upon the tumor cells and do not require for their effectiveness that the tumor be dependent upon the hormonal characteristics of the host These chemotherapeutic agents can be divided into three broad groups The first which is currently receiving the least attention is the attempt to develop substances which will have a deleterious effect ideally a lethal effect on specific kinds of malignant tissue Stilbamidine is the only compound at the present time which has attracted much attention and which can be so classified When used in cases of multiple myeloma administration of the drug is followed by the appearance of basophilic inclusion bodies within the myeloma cells which appear to have the effect of dislocating their nucleoproteins Marked clinical improvement follows in a substantial number of cases It seems doubtful however that the course of the disease is altered beyond the palliative clinical effect Ethylstilbamine a related compound has been tried in an effort to improve upon the results of stilbamidine but it has not been found to be superior to the original compound

Stilbamidine is of more interest than is suggested by the clinical results so far reported because it seems to have a special affinity for these particular malignant cells not explained by general theories of malignancy The inclusion bodies which appear in the myeloma cell do not appear in adjacent normal cells Thus, this one compound suggests a whole new field of potential cancer research it is possible that when the stilbamidine action is better understood, other compounds with a specific effect upon a specific kind of malignant cell will be developed

Cell poisons. Of more immediate interest to the student of bronchogenic carcinoma are the cell poisons These are compounds which have a generally cytotoxic effect, which in sub lethal dosage particularly damages rapidly proliferating tissue Hence, it is theoretically possible with one of these substances to destroy a rapidly growing malignancy without killing the patient in the process The possibility, needless to say, is still academic

Interest in this class of substances arose out of the experiments with mustard gas during and following the first World War The nitrogen mustards, in which nitrogen replaces the sulphur of the mustard molecule, were the first cell poisons to be tested for therapeutic effect upon cancer The action of these substances is still not understood, their particularly violent effect upon living tissue suggests that they interfere, in some way, with the intracellular enzyme systems This would account for their peculiarly virulent affect upon the more rapidly proliferating tissues, normal and malignant Among normal tissues, bone marrow, mucosa (particularly intestinal), and lymphoid tissue are most markedly damaged by nitrogen mustard treatment In the long run the effect on bone marrow is the limiting condition when the drug is used therapeutically Microscopically, the effect of nitrogen mustard on such cells is seen as vacuolization of the cyto

plasm fragmentation of cell nuclei and marked swelling of cells Bastrup Madsen in an *in vitro* study found that the nitrogen mustard severely depressed the mitotic activity of the cells at first but such activity as was present was normal About twenty four hours later long after the mustard had disappeared from the broth mitosis was resumed but was abnormal This second phase is the one of most clinical interest One of the things which make the action of these cell poisons difficult to understand is this delayed reaction in which the significant effect of the poison begins to be seen only after the poison itself has disappeared

Clinically the effect of nitrogen mustard is usually mild local thrombosis at the site of the injection nausea and vomiting a few hours afterward and skin rash in less than half the patients which develops some time later Within a few days a marked and sometimes serious depression in the leukocyte count appears This may persist for as long as three weeks The use of nitrogen mustard is limited by the development of this blood picture which must be watched carefully In animal experiments however it seems that the lethal effect of large doses of nitrogen mustard is primarily due to its effect on gastro intestinal mucosa which is shed massively

Rather oddly the effect of nitrogen mustard upon malignant tissue closely parallels the effect of irradiation not only in the microscopic appearance of cells after treatment but in the spectrum of its usefulness against the various forms of malignancy Thus it is most effective in the treatment of Hodgkin s disease frequently of service in the treatment of lymphosarcoma and at times it may markedly alleviate the symptoms of chronic leukemia Although it parallels radiation in its clinical application however there appears to be distinct differences in the two methods of treatment Most significant is the find

ing that a course of nitrogen mustard frequently re sensitizes tumor cells that have become radio resistant For this reason radiation and nitrogen mustard therapy are frequently alternated

Nitrogen mustard though it parallels radiation therapy in many ways has a distinct advantage in certain instances Animal experiments suggest that it is fixed by the various tissues within a few minutes of injection but its destructive effect is much slower than is the case with irradiation Larger dosage is thus possible Its effect is longer lasting a positive inhibition of cell division may be seen thirty days after injection—almost twice as long as with irradiation Further dosage is more effectively controlled It is thus the treatment of choice in widely disseminated Hodgkin s disease and lymphosarcoma

Early trials of nitrogen mustard in the treatment of bronchogenic carcinoma suggested that not much was to be gained by its use However continued experience has somewhat modified this early pessimism It has not been established that the nitrogen mustards are able to increase life expectancy but subjective improvement is usually obtained and in some instances there may be substantial objective improvement Rather frequently an invalid will become temporarily ambulatory following the treatment On direct inspection by cavernostomy the tumor may at times be demonstrated to have regressed

Dosage is usually 0 1 mg per kilogram of body weight each day for four successive days The usual symptoms are observed—loss of appetite nausea and vomiting and a decrease in the white cell blood count The latter development must be watched closely However the violent reactions to the drug which were encountered in early experience are uncommon at the present time Administration is uncomfortable but it is seldom so intolerable as to require discontinuance of treatment

The greatest positive effect is to be expected in the treatment of undifferentiated carcinoma Literature on the subject frequently refers to the relief of mediastinal symptoms obtained following administration of the drug Adenocarcinoma is least often benefited The findings of Lynch, Ware and Gaensler agree with most reported results According to their classification, 83 per cent of the undifferentiated carcinomas, 50 per cent of squamous carcinomas, 33 per cent of adenocarcinomas, and 11 per cent of the epidermoid carcinomas in their series showed demonstrable objective improvement when treated with nitrogen mustard At times we have felt that there was also some slight increase in life expectancy in cases of bronchogenic carcinoma treated with this drug, but this factor is so difficult to evaluate that we could never be sure that the drug really had this effect

It is certain, however, that in many instances the sense of well being that follows a course of nitrogen mustard is so marked as to justify its use in any instance of inoperable lung cancer in which symptoms are troublesome

"Nitrogen mustard" is hardly a specific description, since over 50 related compounds have been developed which can be so described Only two, however, are in general clinical use at the present time These are methyl bis (B chloroethyl) amine (HN2), and methyl tris (B-chloroethyl) amine (HN3) Limited trials of the other nitrogen mustards have not demonstrated them to be markedly superior to these two Recently, however, several compounds have been announced that can be administered orally, and which seem to have less severe side effects Perhaps the most promising of these new compounds is trisethylene-imino s-triazine (TEM) This compound can be administered intramuscularly or intravenously in a total dose of about 0 15 mg per kilogram of body weight When it is administered in this fashion, its

clinical effect is indistinguishable from the clinical effect of the older nitrogen mustards It can also be administered orally in tablets of 5 mg once or twice daily until a total dose of about 0 4 mg per kilogram of body weight has been given When TEM is administered orally, side effects are less severe and better control of dosage is maintained Its inhibition of the malignancy, however is not more marked than that accomplished by the other nitrogen mustards In a very few clinical trials, its effect upon bronchogenic carcinoma in particular would seem to be considerably less than the effect achieved by the older compounds

Though clinical tests of urethane have been disappointing, *in-vitro* experiments would suggest that it is essentially of more interest than the nitrogen mustards In addition to the depression of mitotic activity, followed by abnormal mitosis, which the mustard demonstrates urethane seems able permanently to arrest cell division in metaphase, a kind of physiological assassination that may in the future be of more interest than the irradiation like effect of the mustards These *in vitro* observations are somewhat uncertain, since a relatively high concentration is required for significant depression of cell action Clinically, urethane has so far been demonstrated to have no more than a pronounced hematologic effect in therapeutic dosage Therefore, its use at the present time is confined to the treatment of the leukemias In the treatment of multiple myeloma urethane may produce remarkable changes in the whole hematologic picture, with marked rise in hemoglobin and a decrease in abnormal serum proteins It is also the treatment of choice in chronic myelocytic leukemia

Dosage for urethane ranges from 2 to 4 grams daily, administered orally, until a total of 200 grams or more, has been reached The blood picture is the factor deter

mining the length of treatment ordinarily urethane is administered until the leukocyte count drops to approximately 20 000/cu mm Thrombopenia is a hazard and toxic symptoms of nausea and vomiting as well as bone marrow depression must be anticipated In spite of much experimental work it has not been demonstrated that urethane can be expected to improve upon the results obtained with nitrogen mustard or radiation therapy

Folic acid antagonists Folic acid antagonists were first applied experimentally in the treatment of malignancy when it was observed that folic acid and its conjugates had the effect of hastening the course of acute leukemia From the beginning the antagonists proved to be significantly effective In a period of five years folic acid antagonists have been used in the treatment of about five hundred known cases of acute leukemia and they have been established as the dr[illegible] and the[illegible]

It [illegible]

[illegible] ing the use of the drug [illegible] a significant improve[illegible] 15 per cent of adults so treated respond satisfactorily although only about Acute lymphocytic leukemia generally responds better than acute myelocytic leukemia

Perhaps one reason for the superior results that have been obtained in children is that they are able to tolerate a larger total dose per kilogram of body weight However there has not been shown to be a correlation between dosage tolerance and response The drug can be administered intramuscularly or orally Dosage may range from 5 mg per day six days a week for a five year old child up to considerably greater doses for adults There is no standard dosage procedure and for this reason oral administration is probably preferred since it affords a more accurate control Once the patient's dosage tolerance has been established the treatment should be continued until

the blood elements return to normal limits, or until toxic reactions force discontinuance of the treatment During the period of treatment, the patient must be watched very closely because the danger of infection is acute

Clinical side effects are apt to be severe, with nausea and vomiting prominent There may be ulceration of the mucous membranes and gastro intestinal hemorrhage, accompanied by severe abdominal pains, megaloblastic anemia, thrombocytopenia, cutaneous eruptions, and other disquieting symptoms Bleeding can sometimes be controlled with toluidine blue or protamine sulphate Special care must be taken to prevent the development of a generalized infection However, prolongation of life at times markedly accompanies clinical improvement One child is still alive 30 months after the onset of the disease —an almost unprecedented life expectancy when the disease is acute leukemia Ultimately, however, the disease can be expected to become refractory to further admin istration of the drug, and the downhill course from that point is usually very rapid

Aminopterin was the first of these folic antagonists, subsequently there has been much effort to develop re lated substances which will improve upon performance of the original At the present time, 4 amino N 10 Methyl PGA is probably the drug of choice

On the whole, limited trials of folic acid antagonists in the treatment of other malignancies have not been en couraging In general, these drugs would seem to be of more potential value in the treatment of sarcomas than in the treatment of carcinomas, although in neither case, except in a few instances, have results been impressive However, there is occasionally evidence of at least some subjective improvement when they are used in the treat ment of bronchogenic carcinoma Since this field of com pounds is still comparatively new, it is possible that an

antagonist effective against lung cancer may be forthcoming sooner or later

The discovery of folic acid antagonists was not the result of any deduction beginning with a theory about tumor tissue, they were discovered experimentally Their specific effect is still somewhat of a mystery They apparently inhibit all cells in their intake of folic acid, this is indicated by the fact that their anti tumorigenic effects as well as their clinical side effects can be suppressed by the administration of the citrovorum factor They are not, then, cell poisons—they are inhibitors Neither can it be said that they are specifically involved in cell growth children receiving the drug continue to grow and mature at normal rates The excitement that the folic acid antagonists have occasioned among cancer research workers is derived from the fact that they apparently specifically inhibit one critical enzyme of a cell from its normal operation

It is theoretically possible, then, to arrest a malignant growth indefinitely The ultimate failure of the drug comes about because the malignant cells are able to adapt themselves to this new situation In experiments, it has been possible to develop leukemias that are to some degree dependent upon folic acid antagonists, the cells are able to convert the antagonists to compounds which can be utilized in place of folic acid There is no reason to believe, however, that other substances with such direct effects upon cell chemistry will necessarily be of temporary effect

All these partially effective and interesting techniques against malignancy are the result of rigorous and determined investigation of possibilities suggested by clinical practice or experimental observation It may well be that such procedures will eventually provide the answers to the control of malignancy On the other hand the effort

of biochemists and pathologists to understand the basic unit of growth, the cell, in the first place, and to understand the peculiar properties of the malignant cell in the second, are slower but more certain This kind of research is directed to that desideratum of cancer control, a chemotherapeutic agent with a deleterious effect upon malignant tissue specifically, and not to a cell poison which indiscriminately attacks all rapidly proliferating tissue A scientific definition of malignancy must ultimately be phrased in terms of the abnormal enzyme pattern which distinguishes the malignant cells from the normal, and is responsible for the clinical characteristics of the tumor

Interest in folic-acid antagonists arises from the fact that, with these compounds, the two approaches to the problem of malignancy seem to be drawing together Folic acid antagonists are not cell poisons, they are enzyme inhibitors They operate imperfectly, but they operate in the same general way that biochemistry assumes the ideal chemotherapeutic agent against cancer will operate For this reason they are one of the most promising developments in modern medicine

Irradiation therapy. Something should be said of the treatment of bronchogenic carcinoma by irradiation Everyone agrees that it offers no hope at all of cure, or marked increase in life expectancy, *but everyone agrees* that it will relieve to a considerable extent the pain of chest wall and mediastinal nerve involvement On the other hand, whether or not there is a sufficient clinical improvement and increase in life expectancy to make its use standard procedure in all inoperable cases has been debated for thirty years Our own judgment is that it should not be so used At times it seems to clear occluded bronchi, with temporary relief of atelectasis and a general improvement in the condition of the patient A marked decrease in the size of the tumor has also been reported at

times by roentgenological evidence The patient may briefly have the definite conviction that he is getting better It is our feeling that much of this is illusory Those studies of the problem which have most carefully provided controls almost uniformly indicate that there is little or no increase in life expectancy The x ray treatments may benefit adjacent infection but only fleetingly and it is to this that the reduction in tumor size and the clearing of the bronchi are due in the majority of patients

In short it is our opinion that the objective improvement achieved by a course of irradiation is not sufficient to justify the disadvantages of these treatments in the usual patient The observed emotional changes that sometimes are occasioned by such treatments overshadow the increase in life expectancy that may or may not be gained Ideally x ray should be reserved for the treatment of symptoms due to nerve or bone involvement In such instances it can be of material benefit This is not entirely the physician's decision however When the patient or the patient's relatives insist upon roentgen ray treatments they cannot be denied

The fundamental research by radiologists is becoming increasingly evident in clinical application Roentgen ray therapy has been judged by many to be still in its early stages of development

Conclusion | 8

MUCH of the progress that has been made in medicine in recent years has been due to the application of scientific techniques and scientific methods to medical problems The gain has been undeniably large On the other hand this development would seem to be an unfortunate consequence The central position of the physician is endangered by the scientific procedures which have been designed to aid him While there is no foreseeable limit to the benefits to be derived from science, this scientific element must not be allowed to overshadow the art of medicine in the care of the human being There can be no substitute for the basic functions of the physician the ultimate evaluations required of him are beyond the reach of scientific method

This problem is apparent in almost every aspect of so complex a subject as bronchogenic carcinoma For example, etiologic studies of this disease have been taken over, very largely, by specialists who are often not practicing physicians This specialization will undoubtedly contribute much to our knowledge of etiology But the practicing physician cannot abandon interest in the subject because much of the work has been taken over by biochemists and other specialists Aside from the etiologic facts immediately relevant to diagnosis, such as age and sex predilection, etiologic theory is a necessary back

ground to a real understanding of the disease The discouraging record to date in the diagnosis of bronchogenic carcinoma perhaps reflects a tendency to approach diagnosis mechanically

On the basis of present diagnostic and surgical techniques, it is possible to increase substantially the percentage of cures over the present rate The problem is not so much one of improved diagnostic techniques, but an earlier application of those techniques now available Early diagnosis of lung cancer depends upon a thorough application of basic medical procedures particularly the physical examination and analysis of the patient's history, in the light of an understanding of the protean possibilities of the malignant process Our problem has been the delay that occurs *before* the advanced diagnostic methods are applied

Of course, major diagnostic problems remain even after the patient has been referred for further study There is no infallible diagnostic technique and most effective use of roentgenology, bronchoscopy, and so forth, demands a maximum of cooperation between the physician and the specialist, and the utmost flexibility In the great majority of instances, morphologic proof of the disease will be possible by means of bronchoscopy and cytology It is hoped that the simplicity and ease of the latter technique will lead to its extensive use in the diagnosis of patients with minimal chest symptoms

We believe that the physician must re-assert his ultimate responsibility for the treatment of the patient after diagnosis is made It devolves upon the physician, not the surgeon, to exhaust his diagnostic techniques in an effort to prove inoperability, before the patient is actually submitted to surgical procedures The physician must always concern himself with the "total care" of the patient, operable or not, in a way that the surgeon cannot be

expected to do We believe that the physician is obligated to save the patient the ordeal of a major surgical procedure which *cannot materially benefit him*

Until recently, bronchogenic carcinoma was generally agreed to be intractable to any approach other than surgical However, there are an increasing number of reports of benefit obtained by the use of the nitrogen mustards Whether an increase in life expectancy has been demonstrated is questionable, but this drug has apparently proven itself of service upon occasion in alleviating symptoms and improving the general condition of the patient This is perhaps a small contribution to the problem, but it can reasonably be regarded as a token of very great service to come It is not unreasonable to expect that the great amount of attention which chemotherapy has received will ultimately produce an effective chemotherapeutic agent for the treatment of malignancy Meanwhile the physician must do the best he can with the procedures available, and he must guard his critical personal role against the impingement of impersonal techniques

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